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NITROGEN UPTAKE DURING AIR DIVING

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ABSTRACT

Henry's Law prescribes that the whole-body equilibrium N_2 content will change in proportion to changes in the alveolar N_2 pressure (ΔP_{AN_2}). Thus, during air diving, increases in P_{AN_2} cause proportionate increases in the whole-body equilibrium N_2 content. The resultant respiratory N_2 uptake, $V_{N_2}(t)$, may be expressed as:

$$V_{N_2}(t) = \alpha * \Delta P_{AN_2} * f(t), \quad (1)$$

where α is the whole-body N_2 solubility, ΔP_{AN_2} is computed using the alveolar gas equation, and $f(t)$ is a function of time that defines the whole-body response to a unit step change in alveolar N_2 pressure. The objective of present work was to quantitatively estimate the form and parameters of $f(t)$ based upon experimental measurements of N_2 uptake in man during diving. Such measurements have not been previously reported. A computer controlled closed-circuit breathing apparatus was developed based on our earlier work, and used to measure N_2 uptake in seated resting subjects during dives from sea level to 40 fsw (2.21 ata) for 250 min, 80 fsw (3.42 ata) for 85 min, and 120 fsw (4.64 ata) for 50 min. Each dive was followed by 60 min of O_2 decompression at 30 fsw (1.91 ata). Air-equivalent inspired O_2 pressures were maintained and CO_2 was scrubbed. Decreases in circuit volume corresponding to N_2 uptake (ml STPD) were measured in real-time on a breath-by-breath basis and normalized to body weight. Three subjects (64.5, 71.7, and 95.6 kg) each dived to each depth three times for a total of 27 experiments. Because noise in the data obscured curvature in the N_2 uptake profiles making most profiles appear linear, $f(t)$ was initially chosen to be a first-order linear equation of the following form:

$$f(t) = \beta_0 + \beta_1 t \quad (2)$$

Equation (2) was fit to data from each depth after substitution into Eq. (1). N_2 uptake rate-solubility products ($\alpha\beta_1$, $\text{ml}^2 / \text{kg}^2 \cdot \text{atm} \cdot \text{min}$), which could not be separated in this formulation, were 0.056 ± 0.000 at 2.21 ata, 0.114 ± 0.001 at 3.42 ata and 0.126 ± 0.004 at 4.64 ata. All intercept values, $\alpha\beta_0$, were less than $2.5 \text{ ml}^2 / \text{kg}^2 \cdot \text{atm}$. The significantly lower rate-solubility product ($\alpha\beta_1$, $p < 0.05$) at 40 fsw suggested a trend toward saturation during the longer 2.21 ata dives. Accordingly, Eq. (3), which accommodates saturation behavior was fit to the data at each depth after substitution into Eq. (1).

$$f(t) = (1 - e^{-kt}). \quad (3)$$

A satisfactory fit was achieved for 2.21 ata data, but convergence was not obtained for 3.42 and 4.64 ata data due to lack of curvature in those profiles. When Eq. (3) was fit to the data from all depths, however, convergence was achieved yielding $\alpha = 0.01268 \pm 0.00013 \text{ ml/gm} \cdot \text{atm}$ (N_2 solubility in water at 37°C is $0.01199 \text{ ml/gm} \cdot \text{atm}$) and half-time, $\tau = 66.76 \pm 0.02 \text{ min}$ ($\tau = 0.693 / k$) and indicating conformance to Henry's Law. Under the conditions studied, and to within present methodological precision: (1) a single semi-exponential equation correlates measured whole-body N_2 uptake at pressures from 2.21 to 4.64 ata; (2) whole-body N_2 uptake is kinetically the same at different pressures; (3) and pressure dependence of N_2 uptake is adequately described by Henry's Law.

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LIST OF ABBREVIATIONS

ata	atmospheres absolute
BTPS	body temperature pressure saturated
FRC	functional residual capacity
fsw	feet of sea water
IC	Inspiratory capacity
lpm	liters per minute
PET _{CO₂}	end-tidal carbon dioxide partial pressure
PI _{CO₂}	inspired carbon dioxide partial pressure
PAN ₂	alveolar N ₂ pressure
PI _{O₂}	inspired oxygen partial pressure
Pt _{O₂}	tissue oxygen partial pressure
RMV	respiratory minute volume
STPD	standard temperature pressure dry
tP _{N₂}	tissue nitrogen partial pressure
V _{DS}	dead space volume
V _{N₂} (t)	nitrogen uptake
V _T	tidal volume

1. INTRODUCTION

1.1 Background

A diver breathing compressed air absorbs nitrogen (N_2) during compression and at pressure and eliminates it during and after decompression. Since most of this gas passes through the lungs, measurement of respiratory nitrogen exchange can provide both volumetric and kinetic information about N_2 that is absorbed or eliminated at the whole-body level. Previous N_2 exchange experiments were limited by focusing on N_2 elimination while neglecting N_2 uptake (1, 3-9). Both uptake and elimination data are needed to address issues such as the symmetry of nitrogen uptake and elimination, the failure of which might be indicative of in vivo bubble growth during and after decompression. These measurements can help improve our understanding of the body's physiological responses to the stresses of hypo/hyperbaric exposure. While the evidence suggests that decompression pain is associated with small volumes of N_2 in slow tissues (2), the possibility remains that larger N_2 volumes stored in faster tissues may play a role in more serious decompression sickness (DCS), particularly in association with large volumes of venous gas emboli.

N_2 elimination has been measured in oxygen breathing subjects at sea level (3-5), at pressures up to 2.5 ata (9), during decompression (6-8), and in air breathing subjects after air diving (1), but measurement of nitrogen absorption at pressure has never been reported. Present theory holds that whole-body inert gas uptake should be governed by Henry's Law. Thus, we assume that the time course of N_2 uptake can be described by Henry's Law multiplied by a kinetic function, $f(t)$, with a range of zero to one as time t , increases from zero to infinity. With this function and appropriate values of its parameters, the total N_2 volume absorbed, as well as the kinetics of N_2

absorption, during air diving could be estimated. In present work such functions were derived from respiratory nitrogen uptake measurements obtained from normal resting subjects breathing air from a closed-circuit rebreather. Inspired O₂ partial pressure was maintained and CO₂ was scrubbed. Therefore, decreases in the gas volume within the circuit represented N₂ uptake at depth. The potential effects of absolute pressure and O₂ partial pressure on the proposed kinetic function were ignored. Experiments were performed for three depth / time dive profiles and were repeated 3 times by each of three subjects.

1.2 Hypothesis and Objectives

According to Henry's Law, the equilibrium volume of gas dissolved per unit volume of liquid is proportional to the partial pressure of the gas in contact with that liquid (10, 15).

$$V_{\text{Gas}} = \alpha * P_{\text{Gas}}$$

During air diving, increases in alveolar N₂ pressure (ΔP_{AN_2}) cause proportionate increases in the whole-body equilibrium N₂ content. The resultant respiratory N₂ uptake, $V_{\text{N}_2}(t)$, may be expressed as:

$$V_{\text{N}_2}(t) = \alpha * \Delta P_{\text{AN}_2} * f(t) \quad (1)$$

where α is the whole-body N₂ solubility, ΔP_{AN_2} is the change in alveolar nitrogen pressure and $f(t)$ is a function of time that defines the whole-body response to a unit step change in alveolar N₂ pressure. The objective of this work was to show that Eq. (1) can be used to correlate measured whole-body N₂ uptake in man and quantitatively estimate the form and parameters of $f(t)$.

2. METHODS

Measurement of respiratory nitrogen exchange with a closed-circuit rebreather is based on the assumption that uptake of nitrogen by a subject's body is reflected in the loss of volume from the rebreather counterlung. When CO₂ is absorbed as it is produced and O₂ is replaced as it is consumed, the rebreather is an open system for these gases. Thus, changes in metabolic rate, respiratory quotient, or amount of physically dissolved O₂ do not affect the volume of gas in the rebreather. As the whole-body content of dissolved O₂ changes with inspiratory O₂ partial pressure, only transient errors in measured O₂ consumption can occur.

2.1 Subjects

The study was approved by the Duke University Institutional Review Board (# 024-91-1R2, Appendix A). Three healthy, nonsmoking male volunteers gave written informed consent to participate in each experiment for which they received \$100 in compensation. Each subject was familiarized with the experimental environment and procedure before testing. All had normal chest x-rays and diving physicals within one year of testing as per protocol for exposure to hyperbaric pressure. Body fat measurements were performed by water immersion which incorporated vital capacity measurements obtained from pulmonary function tests. A breakdown of subject physical characteristics is included in Table 1.

Table 1
Subject Information

Subject	Sex	Age	Height (cm)	Weight (kg)	Body fat (%)	Vital Capacity (L)
CM	M	34	185	95.567	0.315	5.71
PF	M	37	173	64.468	0.100	5.58
TA	M	34	165	71.732	0.179	5.35

2.2 Experimental Protocol

Figure 1 summarizes the experimental protocol. The three subjects performed each dive three times to examine the consistency of gas uptake. A tender from the laboratory staff accompanied the subject at all times. An experiment consisted of a control period at the surface, an equipment equilibration period at depth, compression and transfer of the subject and tender to the experimental chamber using an adjoining chamber, a N₂ uptake measurement period, and a decompression period.

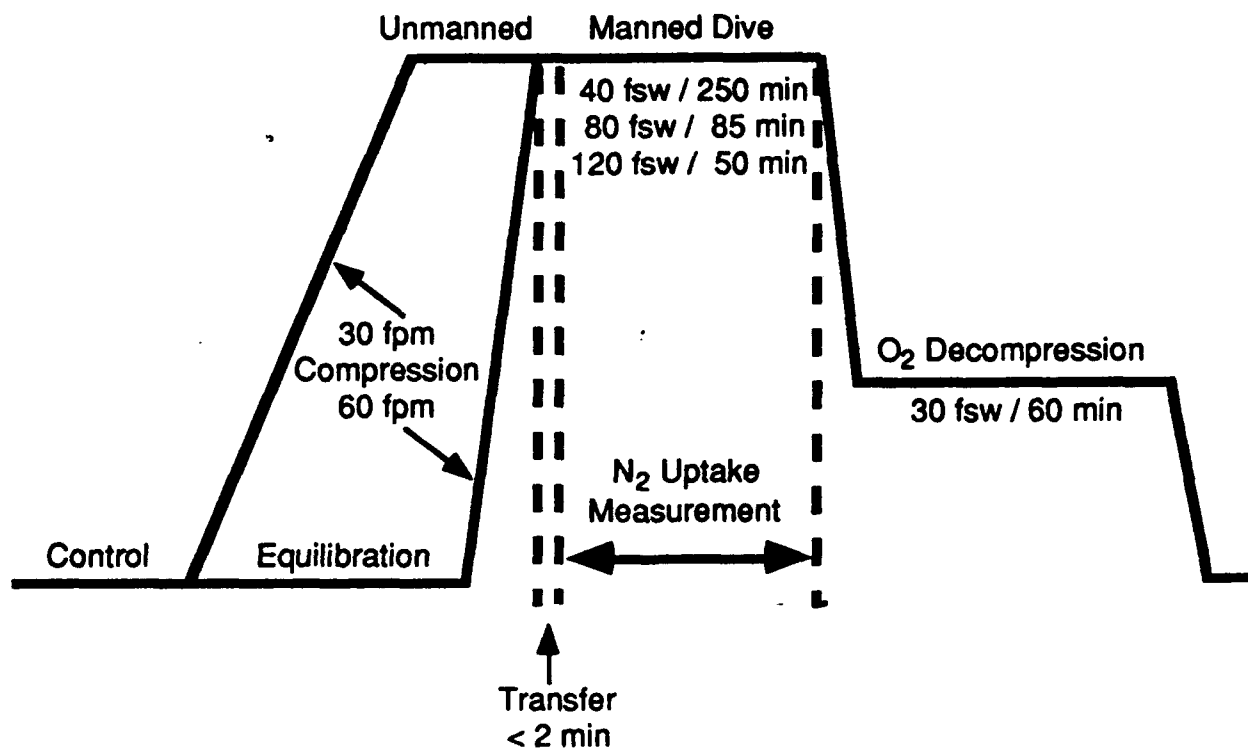


Figure 1: Experimental protocol

2.2.1 Surface control procedure

The surface control period (~ 45 min) served to evaluate system performance and allowed for water vapor saturation of the gas within the measurement system. The subjects assumed a semi-reclined position in the experimental chamber, put on nose clips, and breathed through a mouthpiece connected to the N₂ exchange measurement system. Air was breathed throughout the control period. Approximately 15 minutes were allowed for temperature equilibration and water vapor saturation. System performance was evaluated during the final 30 minutes of the surface control procedure. The N₂ volume within the closed-circuit rebreather should not change when measuring N₂ exchange in normal human subjects without recent hypo/hyperbaric exposure (subjects were restricted from hyperbaric exposure for 48 hours prior to each experiment). Changes in volume measured during the surface control period represented system measurement error. Based on unmanned system tests discussed in Results, N₂ volume changes from -1.1 to +3.1 ml/min over the last 30 min of the surface control procedure were deemed acceptable [Section 3.1.3].

2.2.2 Equipment equilibration at depth

N₂ uptake measurements during compression were not attempted due to the large temperature transients which occurred with compression. Thus, the subject was removed from the chamber after completion of the surface control period to compress the system to the test depth. The measurement system was attached to a syringe pump and air was added to the closed-circuit system during compression . Gas was circulated with the syringe pump until pre-dive temperatures and oxygen sensor output stabilized (oxygen sensor output varied with temperature). This equilibration period lasted approximately 45 min.

2.2.3 Transfer procedure

Once oxygen, volume, and temperature values were stable for 5 min, the subject and tender were compressed to the test depth (≈ 60 fpm or 1.8 atm/min) in an adjacent chamber. Once the transfer chamber reached the pressure of the experimental chamber, hatches connecting the chambers were opened and the subject and tender entered the experimental chamber. The pump was detached, the subject assumed the same position as during the surface control procedure and began breathing from the N_2 exchange measurement system (< 2 minutes from arrival at the test depth). Data recording was initiated at this time.

2.2.4 N_2 exchange measurements

Subjects rested while breathing air from the N_2 exchange measurement system for 50 minutes at 120 fsw (4.64 ata), 85 minutes at 80 fsw (3.42 ata), or 250 minutes at 40 fsw (2.21 ata). The tender breathed an enriched oxygen mixture (32% O_2 at 3.42 and 4.64 ata or 36% O_2 at 2.21 ata) to lower N_2 uptake at pressure.

2.2.5 Decompression procedure

All experiments were followed by 60 min of decompression at 30 fsw (1.19 ata) during which both the subject and tender breathed 100% O_2 . The bottom times were selected using methods described in Appendix B. The DCS risk was estimated to be less than 0.01%. After decompression, subjects were monitored for precordial bubbles by Doppler (Techno Scientific, Woodbridge, Ontario, Model DBM 9008). Because none of the subjects had bubbles after their initial dive to each depth, Doppler monitoring was not done on repeat experiments.

2.3 Equipment

2.3.1 Spirometer and breathing circuit

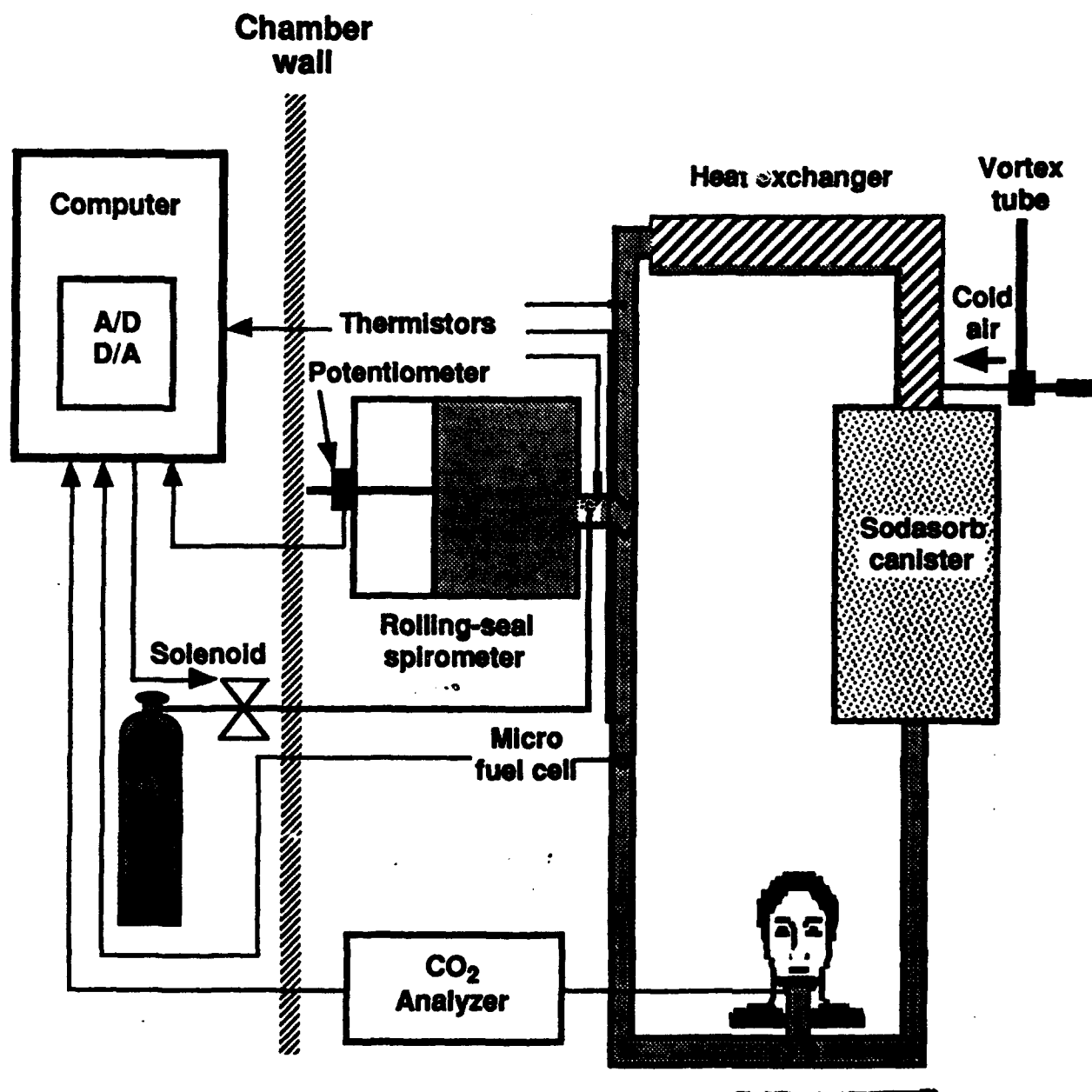


Figure 2 : Closed-circuit rebreather used to measure N₂ uptake

The closed-circuit rebreather shown in Figure 2, was based upon a 10 liter rolling seal spirometer (Sensormedics, Model 922). A potentiometer attached to the piston of

the spirometer provided voltage output to the computer. The spirometer was calibrated with a 3 liter syringe (Collins, Model M-20). A temperature probe (YSI, Model 710) was inserted into the input/output duct of the spirometer to provide data for temperature correction of the measured volumes. The thermistor (time constant = 0.3 sec) was calibrated from 17 - 37 °C. Tidal volume (V_T) was corrected to BTPS as follows:

$$V_T = (V_{\max} - V_{\min}) * T_{\text{Cor}} * WV_{\text{Cor}}$$

where:

$$\begin{aligned} V_{\max} &= \text{Maximum volume during breath} \\ V_{\min} &= \text{Minimum volume during breath} \\ T_{\text{Cor}} &= \text{Temperature correction} = 310.0 / (273.0 + T_S) \\ T_S &= \text{Spirometer temperature} \end{aligned}$$

$$WV_{\text{Cor}} = (P_{\text{ata}} - PH_2O) / (P_{\text{ata}} - PH_2O_{\text{BT}})$$

where :

$$\begin{aligned} P_{\text{ata}} &= \text{Barometric pressure in ata} \\ PH_2O &= \text{Ambient water vapor pressure in ata.} \\ PH_2O_{\text{BT}} &= \text{Ambient water vapor pressure in ata at body temperature} \\ &= 47 / 760 \text{ atm} \end{aligned}$$

Ambient water vapor pressure was determined, assuming saturation, by using the following third-order polynomial:

$$PH_2O = (2.47488 + (0.65949 * T_S) - (0.00712 * T_S^2) + (0.00059 * T_S^3)) / 760.0$$

This equation was obtained from regression analysis of water vapor pressures at temperatures from 12 to 42°C tabulated in Ref.11.

Maximum and minimum volumes were determined using a peak detection software routine to obtain V_T . Respiratory rate was determined by measuring the time between maximum volumes or end-exhalations. Respiratory minute volume (RMV) was calculated as: $RMV = V_T \times \text{respiratory rate}$

Flow was directed into and out of the spirometer via a T-shaped two way valve (Hans Rudolf, Model 2700). This valve provided an entry point for the spirometer temperature probe and an oxygen addition input. Another valve (Hans Rudolf, Model

2700) served as the mouthpiece valve. A silicon rubber SCUBA mouthpiece was attached to a microbial filter (Pall Biomedical, Model P30S) which was then attached to the valve. These valves were chosen for their low dead space (90 ml), large bore (28.6 mm = $1 \frac{1}{8}$ in.), and low resistance (0.8 cm H₂O / lpm). Breathing resistance, which increases with density of the breathing gas, was minimized by ensuring that all portions of the breathing loop had an inner diameter (ID) of at least 28.6 mm. The components of the breathing circuit were connected using 35 mm ($1 \frac{3}{8}$ in.) ID smooth bore tubing (Hans Rudolf, Model 9039) .

2.3.2 Computer

Data were recorded on a DEC MINC 11/03 computer on a breath-by-breath basis, triggered at end exhalation. The following variables were sampled at 50 Hz by a 12 bit A/D board installed in the MINC 11/03: inspiratory temperature (°C), expiratory temperature (°C), spirometer temperature (°C), inspiratory O₂ partial pressure (ata), end-tidal CO₂ (torr), volume (ml), and peak-peak mouthpiece pressure (cm H₂O). Input voltage range was +5 to -5 volts, allowing 2.44 millivolt resolution. The controlling software was written in Fortran IV. Subroutines were developed for system calibration and oxygen control and data acquisition, display, and storage.

2.3.3 Oxygen pressure control

A micro fuel cell (Teledyne Analytical, Model B7W) was used as an oxygen sensor to monitor the inspired oxygen partial pressure (P_IO₂). This cell had a response time (0 - 90%) of 7 seconds and was mounted in a $1 \frac{1}{4}$ in. (31.8 mm) copper "T" downstream to the spirometer input/output port. The fuel cell surface was exposed to the gas flow but did not obstruct the breathing loop. The output from the fuel cell was input into a current-voltage converter/amplifier with hardware temperature compensation (YSI, Model 710). The thermistor penetrated the copper tee in close proximity to the O₂

sensor. The O₂ sensor was calibrated at each depth against an O₂ analyzer (Applied Electrochemistry Inc., Model S3A/N-37M). Addition of O₂ (99.999% USP O₂) was directed by a computer-controlled solenoid valve connected to a regulator (National Welders, Model HPTD) on a O₂-filled G-cylinder. O₂ flowed from the solenoid through a 60 micron filter and a 0.0135 in. (0.34 mm) orifice designed to achieve a critical flow of 6 liters per minute (12). O₂ flow calibration was performed at each depth by pulsing the solenoid for 1 minute and measuring the increase in volume. As the P_iO₂ dropped below the user defined set point by an input amount, the solenoid was fired for 1.0 second, adding approximately 100 ml of O₂. Comparison of the P_iO₂ to the set point was done every other breath to allow for gas mixing delays. Computer control was achieved using output from a digital I/O board within the MINC 11/03 computer. To fire the solenoid, the least significant bit of the 8 bit I/O port was set high (+4.5 volts) and sent to the input of a 12 volt solenoid driver.

2.3.4 Carbon dioxide control

At the end of each experiment, a gas sample was drawn from the inspired side of the breathing loop by a carbon dioxide analyzer (Beckman, Model LB2) to confirm that exhaled CO₂ had been completely scrubbed from the rebreathing circuit. The CO₂ analyzer (response time = 0.1 sec) was calibrated at each depth using Primary Standard calibration gases: 8.00% CO₂ at the surface; 4.00% CO₂ at 40 fsw; and 2.52% CO₂ at 80 and 120 fsw. Exhaled flow was directed through the sodasorb canister (Collins, Model 21377). The sodasorb chemically binds CO₂ via the following reaction (13):

- i.) $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$
- ii.) $2\text{H}_2\text{CO}_3 + 2\text{Na}^+ + 2\text{OH}^- + 2\text{K}^+ + 2\text{OH}^- \rightarrow 2\text{Na}^+ + \text{CO}_3^{2-} + 4\text{H}_2\text{O}$
- iii.) $\text{Ca}(\text{OH})_2 + \text{H}_2\text{O} \leftrightarrow \text{Ca}^{++} + 2\text{OH}^- + \text{H}_2\text{O}$
- iv.) $2\text{Ca}^{++} + 4\text{OH}^- + 2\text{Na}^+ + \text{CO}_3^{2-} + 2\text{K}^+ + \text{CO}_3^{2-} \leftrightarrow 2\text{CaCO}_3 + 2\text{Na}^+ + 2\text{OH}^- + 2\text{K}^+ + 2\text{OH}^-$

The reaction is exothermic, yielding 13.5 kcal/mole CO_2 , thus heating the exhaled gas. Heat build-up necessitated the use of a heat exchanger at the downstream end of the Sodasorb canister. The cold air output from a vortex tube (Vortec, Model 106) was directed down copper tubing wrapped around the circuit tubing exiting from the Sodasorb canister and entering the spirometer. This allowed for maintenance of circuit temperature. Water, a byproduct of the above absorption processes, reduced canister volume by ~ 60 ml / hr (13).

2.3.5 Nitrogen Volume Calculation

The volume of nitrogen in the apparatus was calculated at end exhalation of each breath using Eq. 4.

$$V_{\text{N}_2} = V_{\text{Tot}} * F_{\text{I}_{\text{N}_2}} \quad (4)$$

where:

$$V_{\text{Tot}} = V_{\text{T}} + V_{\text{DS}} \text{ and}$$

$$F_{\text{I}_{\text{N}_2}} = \frac{(P_{\text{B}} - P_{\text{I}_{\text{O}_2}} - P_{\text{H}_2\text{O}})}{P_{\text{B}}}$$

where V_{N_2} = nitrogen volume (STPD), V_{Tot} = total volume (STPD), $F_{\text{I}_{\text{N}_2}}$ = inspired nitrogen fraction, P_{B} = barometric pressure (ata), $P_{\text{I}_{\text{O}_2}}$ = inspired oxygen partial pressure (ata), $P_{\text{H}_2\text{O}}$ = water vapor pressure (ata), V_{DS} = dead space volume

System dead space volume was 7.5 L as determined by summation of the measured water volume or specified dead space for each circuit component.

2.3.6 Ancillary parameters

A fitting was placed in the mouthpiece valve to accommodate $\frac{1}{8}$ in. (3.2 mm) ID tubing connected to a pressure transducer (Validyne, Model MP45-871). The pressure transducer was used to record peak-peak mouthpiece pressure, an indicator of breathing resistance (14). The mouthpiece pressure was calibrated from 0 - 40 cm H₂O pressure using an electronic manometer (Setra Systems Inc., Model 339-1).

2.4 Data Analysis

2.4.1 Volume measurement error

Small individual error sources can combine to produce a large overall error in calculated N₂ uptake. These errors (e.g. P_{iO₂} control, volume measurement, lung volume changes) tend to be random and contribute only to a relatively large scatter in the measurements. A best-fit curve to such data effectively eliminates random scatter.

Measurements of STPD volume at elevated pressure are degraded as a consequence of Boyle's law. The spirometer measures the actual gas volume at ambient chamber pressure. When this volume is adjusted to STPD, adjustments are also made to any errors that were present. For measurements made at altitude, this reduces the error, while errors become larger for measurements made at elevated pressure (Table 2). Thus, a measurement error of 1 ml at 120 fsw (4.64 ata) will appear as 4.64 ml when adjusted to STPD.

Table 2
Effect of Boyle's Law on volume measurement error

Absolute Pressure (ata)	1 ml error converted to STPD
0.5 (18K feet)	0.5 ml
1.0	1.0 ml
2.21 (40 fsw)	2.21 ml
3.42 (80 fsw)	3.42 ml
4.64 (120 fsw)	4.64 ml

The various methods of data representation listed below were attempted to minimize the volume measurement errors.

2.4.2 Breath-by-breath data acquisition

The raw data consisted of results from nitrogen exchange measurements made on a breath-by-breath basis. The point for each breath was obtained by multiplying the total system volume by the measured nitrogen fraction at end-exhalation and subtracting the result from the initial computed N₂ volume. All computed changes in nitrogen volume were corrected to STPD in real time.

2.4.3 Minute averaging, smoothing, and FRC referencing

The nitrogen volume changes were recalculated for successive one minute periods and by smoothing (using a quadratic convolute with a 25-point window) in an attempt to reduce scatter and time phase differences between volume and oxygen measurements.

Another attempt to reduce scatter due to lung volume changes was to use functional residual capacity (FRC) as a reference for the nitrogen volume change calculation. Subjects were given an event marker and told to mark the breath during which they achieved FRC. FRC maneuvers were performed at one minute intervals designated by audible alarm. Nitrogen elimination has been measured using a similar

system of recording closed-circuit volume changes between successive breaths at FRC (1).

The above attempts failed to significantly reduce scatter. Therefore, analysis was performed on the raw data.

2.4.4 Inspiratory capacity referencing

Since the largest component of measurement noise was due to lung volume changes, system nitrogen content was calculated at the beginning and end of each experiment during maximal inspiration (IC), which is a reproducible fixed volume (14). The spirometer volume was noted during three repeated maximal inspiratory maneuvers at the start and end of each experiment. The change in system volume between start and finish was an independent measure of respiratory inert gas exchange and was used to verify the accuracy of the breath-by-breath measures.

2.5 Statistical methods

A first-order linear regression was applied to the raw data for each experiment. The slopes of the regression lines were averaged for each subject and depth and multiple comparisons were made by paired two-tailed t-test. The data were transformed from measured system volume changes to nitrogen uptake and normalized for subject weight and alveolar N_2 pressure change. Both linear and non-linear regressions were applied to the normalized data at each depth and to all data.

3. RESULTS

3.1 Control experiments

A series of experiments was conducted to quantify system resolution and accuracy. System resolution was defined as the smallest nitrogen volume change that could be resolved while system accuracy was defined as the error from a known change in nitrogen volume.

3.1.1 Unmanned system resolution

Static volume resolution was determined at the surface by repeatedly injecting known volumes of air into the system using a 3 L calibrated syringe. Volumes measured by the spirometer were reproducible to ± 3 ml for successive 3 L changes in volume, over the full range of spirometer volume capacity (0-3, 3-6, and 6-9 L). Also, progressively smaller volumes of air were introduced into the system using 20, 10, and 5 ml syringes. The system accurately recorded changes in volume down to 3 ml.

To determine dynamic resolution at the surface, the syringe pump was connected to the system, filled with air, and allowed to equilibrate. Air was extracted from the system via glass syringe at five minute intervals in 5, 10, and 20 ml increments. Measured decreases in nitrogen volume were within 9% of known decreases for 5 ml air extractions and within 4% of known decreases for 10 ml and 20 ml air extractions.

Nitrogen volume change was recorded during breathing simulations at the surface (1 ata), at 30 fsw (1.91 ata) and at the test depths: 40 fsw (2.21 ata); 80 fsw (3.42 ata); and 120 fsw (4.64 ata). The rebreathing circuit was filled with air at the surface and attached to the syringe pump, which was set to a tidal volume of 500 ml at 15 breaths per minute (bpm). The chamber was compressed to the test depth and after approximately 45 minutes of temperature equilibration time, nitrogen volume changes

were recorded. Boyle's law adjustments of measured volumes amplified the errors when expressed in terms of standard temperature and pressure (STPD). This is evident in Figure 3 where nitrogen volume changes measured over 5 min periods at each depth are shown. Measurements were scattered at the surface over a range of ± 8 ml, whereas values at 120 fsw were scattered over a range 5 times greater than at the surface.

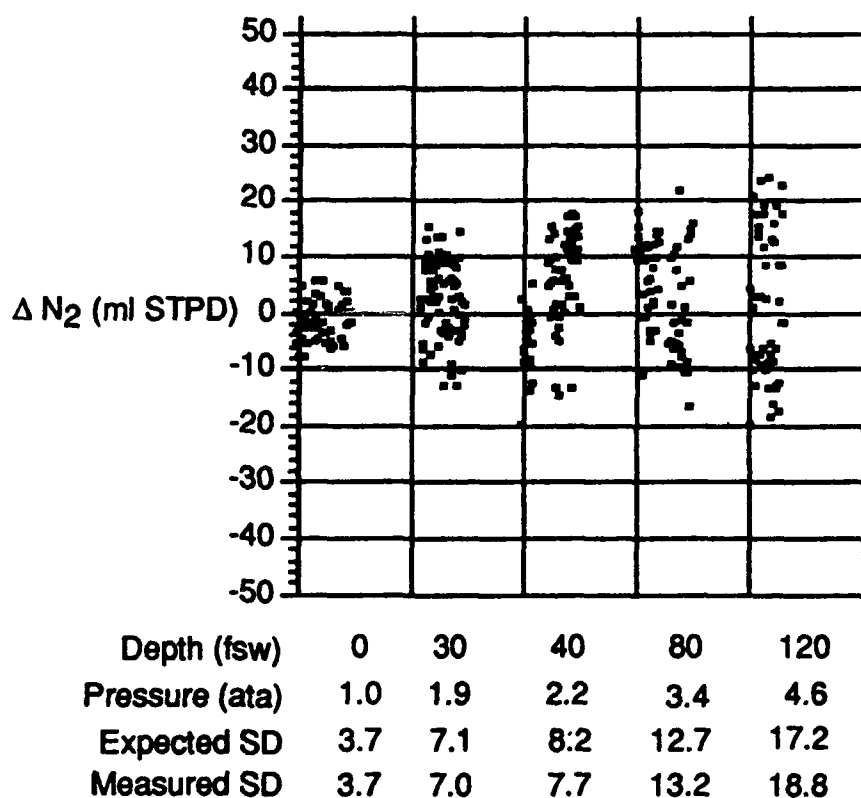


Figure 3 : Effect of STPD conversion on volume resolution due to Boyle's Law.
Expected SD based on SD = 3.7 at 1 ata

Determination of system volume resolution at the surface, therefore, defined the system's best resolution. The scatter of measured volumes about an actual volume is representative of the volume resolution.

Volume measurement in this experiment was dependent upon syringe pump stroke, volume measurement reproducibility, and system integrity. System integrity

was tested by applying a static internal pressure (± 10 cm H₂O) greater than would be produced during an experiment with a resting human in the loop, and calculating the leak rate. This leak rate was under 0.03 ml/min. As static volume resolution had been found to be ± 3 ml, the remaining scatter was attributed to random variation in the syringe pump stroke volume about ± 5 ml maximum.

3.1.2 Unmanned measurement errors

Systematic error can also be represented as the rate of nitrogen volume change, or the slope (ml/min) of the linear regression of the change in system nitrogen volume over time. Experiments using a syringe pump were done to determine volume measurement error. Nitrogen volume change calculations were dependent upon volume, temperature, and oxygen measurements; all possible sources of error. Therefore, by using an unmanned system, oxygen partial pressure, chamber pressure, temperature and water vapor content could be held constant. The breathing circuit was filled with air at the surface and attached to the syringe pump (tidal volume = 500 ml; breathing frequency = 15 bpm). After the initial nitrogen volume in the closed system was calculated, the pump was switched on and changes in system N₂ volume from the initial volume were recorded on a stroke-by-stroke basis. Volume measurement error was determined to be ± 0.03 ml/min STPD since that was the deviation from zero slope (Figure 4 - left panel). This represents the minimum system error because increasing depth magnifies error and measurements on humans introduce still more error from oxygen, temperature, humidity, and CO₂ changes.

When the above experiment was repeated at 4.64 ata, the rate of nitrogen volume change varied from zero by 0.27 ml / min (Figure 4 - right panel). Individual points appear to define several parallel straight lines, perhaps reflecting random changes in pump stroke volume that occurred in discontinuous multiples of ~ 10 ml. These

changes also occurred at 1 ata but were amplified by the Boyle's law correction from 4.64 ata.

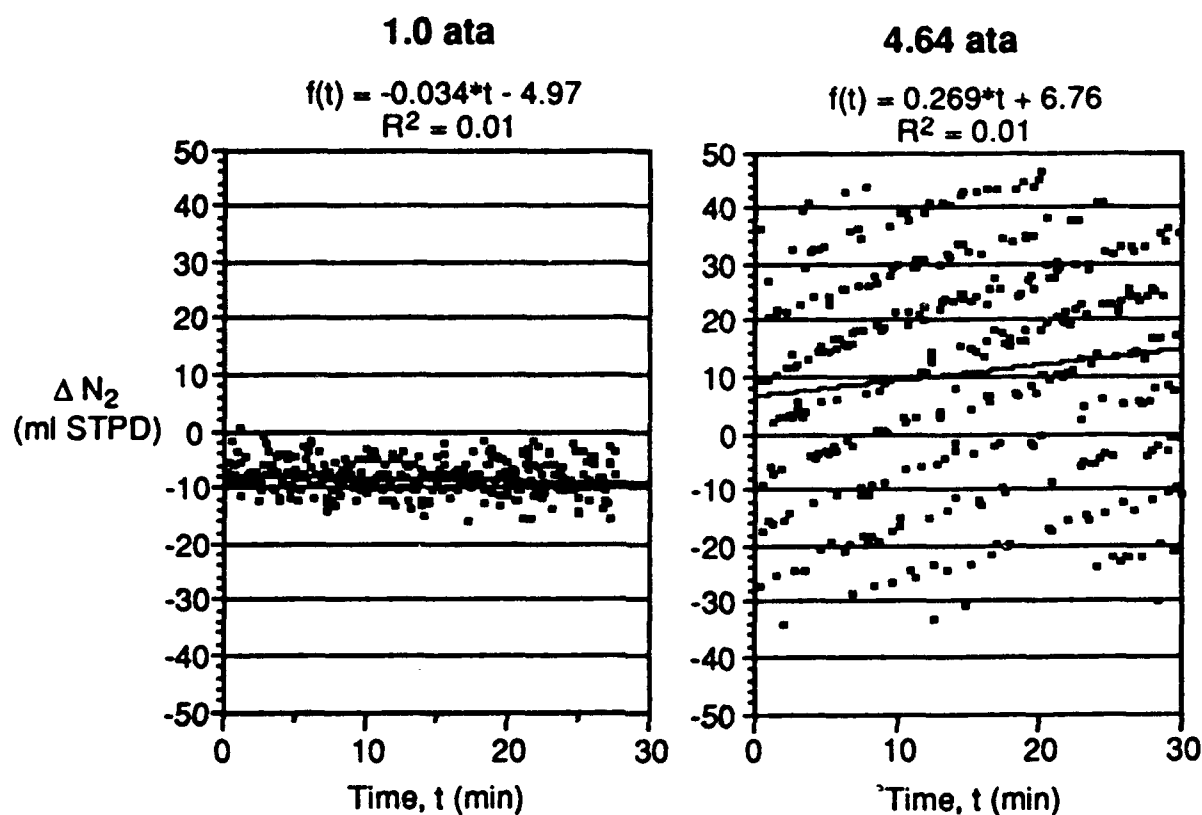


Figure 4 : Unmanned control experiments at the surface (1 ata) and 120 fsw (4.64 ata)

Finally, systematic error was estimated for the unmanned system by measuring the rate of a known system leak that was introduced to simulate N_2 uptake. A measured leak rate of 34.7 ml/min STPD (Figure 5) was within 5% of the nitrogen volume (36.5 ml/min STPD) measured by a 9 L Collins recording vitalometer used to collect the leak outside the chamber.

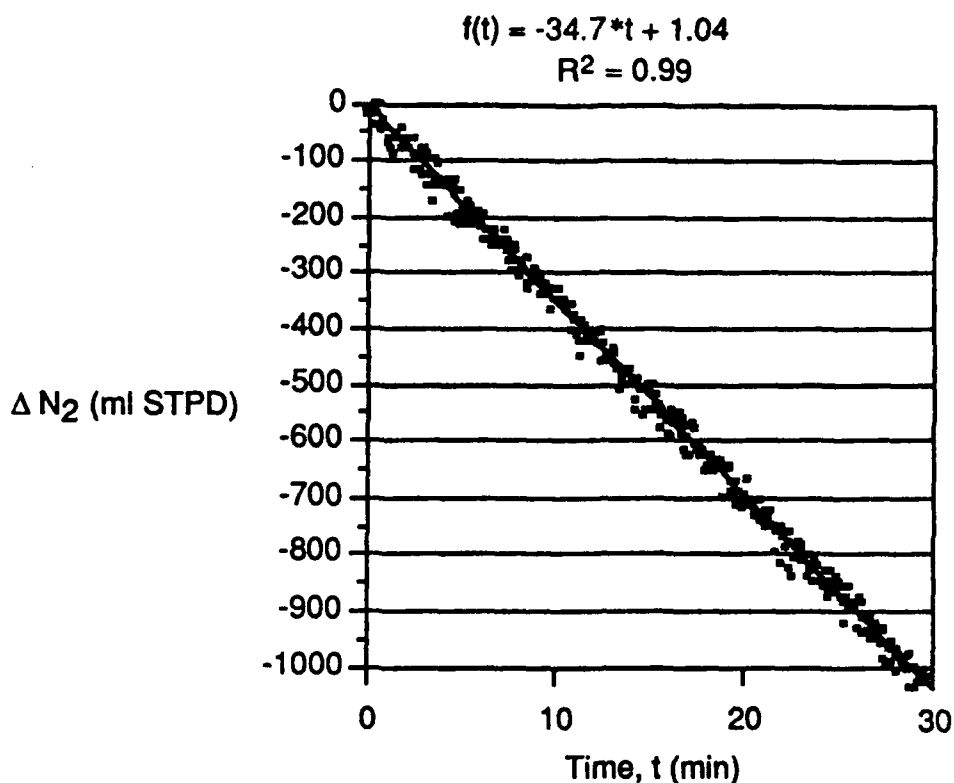


Figure 5 : Unmanned N_2 uptake simulation at 120 fsw (4.64 ata).
Note scale change (y-axis) from previous figures

3.1.3 Manned control experiments

Prior to each nitrogen uptake experiment, a surface control study (~45 min) was performed to evaluate system performance, saturate the breathing loop with water vapor, and add CO_2 to the exhalation limb upstream of the sodasorb canister. Once equilibration had occurred (~15 min), water vapor, CO_2 content, and ambient pressure remained constant, oxygen partial pressure varied around a set point (0.209 ata), and total system volume changed with tidal volume. The amount of nitrogen in the rebreathing system was calculated at the start of the experiment and the change in that volume was calculated on a breath-by-breath basis. When net nitrogen exchange is zero, the change in system nitrogen volume should vary randomly with tidal volume and O_2 pressure. Net nitrogen exchange in subjects restricted from diving 48 hrs prior

to the experiment should be zero. Data were recorded as changes in N₂ volume from the start of the experiment. Figure 6 shows results from a typical surface control experiment. The slope (0.97 ml / min) of the regression line drawn through the N₂ volume changes over time is the mean rate error. The standard deviation for this breath-by-breath data was 150 ml STPD.

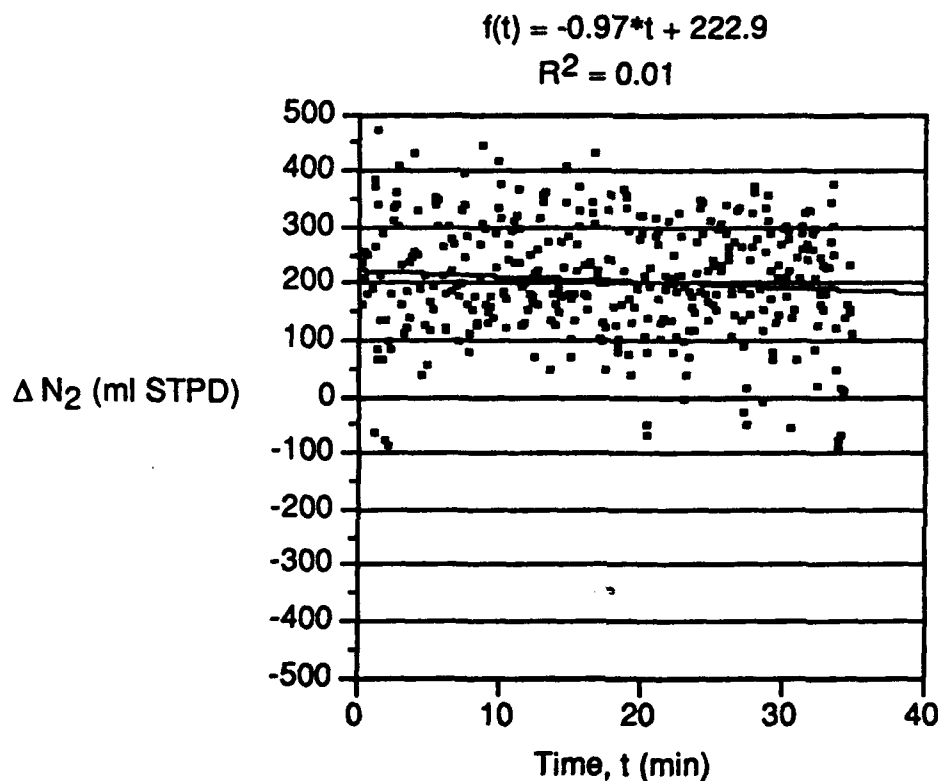


Figure 6 : Manned surface control experiment.

The high mean rate errors and breath-by-breath scatter relative to those in the unmanned controls arise from error sources introduced by the human in the circuit: CO₂ and water vapor in the rebreathing circuit; temperature changes; oxygen consumption and addition, and; tidal volume changes. Manned surface control N₂ volume change rates in the range -1.1 to +3.1 ml/min were considered acceptable. The acceptable range was computed from the maximum unmanned control error (± 0.3 ml/min) + unmanned N₂ error (± 1.8 ml/min) + water accumulation error (+1.0 ml/min).

The water accumulation error comes from water production during CO₂ absorption which occurs at a rate of 60 ml/hr [Section 2.3.4].

3.2 Diving experiments

Nitrogen uptake was studied in a dry pressure chamber with subjects at rest. Oxygen consumption and minute ventilation data are shown in the Tables 3 and 4 below. These data were not recorded at 120 fsw.

Table 3
Mean \pm SD oxygen consumption (ml / kg \cdot min) during N₂ uptake measurements

DEPTH (ata)	SUBJECT A	SUBJECT B	SUBJECT C
1.00	5.11 \pm 0.53	4.40 \pm 0.49	5.93 \pm 0.66
2.21	5.32 \pm 0.07	4.34 \pm 0.16	5.59 \pm 0.60
3.42	5.03 \pm 0.20	3.14 \pm 0.16	5.69 \pm 0.91
ALL DEPTHS	5.14 \pm 0.39	4.38 \pm 0.35	5.79 \pm 0.66

Table 4
Mean \pm SD minute ventilation (lpm) during N₂ uptake measurements

DEPTH (ata)	SUBJECT A	SUBJECT B	SUBJECT C
1.00	11.62 \pm 0.35	14.00 \pm 1.90	14.33 \pm 1.91
2.21	11.50 \pm 0.60	13.20 \pm 0.17	12.30 \pm 1.16
3.42	10.17 \pm 0.15	13.60 \pm 0.36	13.47 \pm 2.84
ALL DEPTHS	11.23 \pm 0.73	13.67 \pm 1.27	13.56 \pm 2.01

Oxygen consumption did not change over time at any depth. Linear regressions of oxygen consumption data over time produced slopes of less than 1 ml/min/min. Minute ventilation dropped an average of 10 ml/min/min during the 2.21 ata for 250 min exposure but not during the 3.42 for 85 min exposure.

Inter-depth and inter-subject comparisons of nitrogen volume changes were performed using the slopes from first-order linear regression of breath-by-breath data. The total N₂ volume change for each experiment was computed as the slope times the duration of the N₂ uptake measurements and as the overall change in system N₂ volume from the start to the end of the experiment (at inspiratory capacity (IC), the reference lung volume). Comparisons of these two values for all experiments are shown in Figure 7. The calculated regression line has a slope close to 1.0 (1.03) indicating that the two methods agree, but the low R² value (0.27) is due to the large amount of scatter in the breath-by-breath measurements.

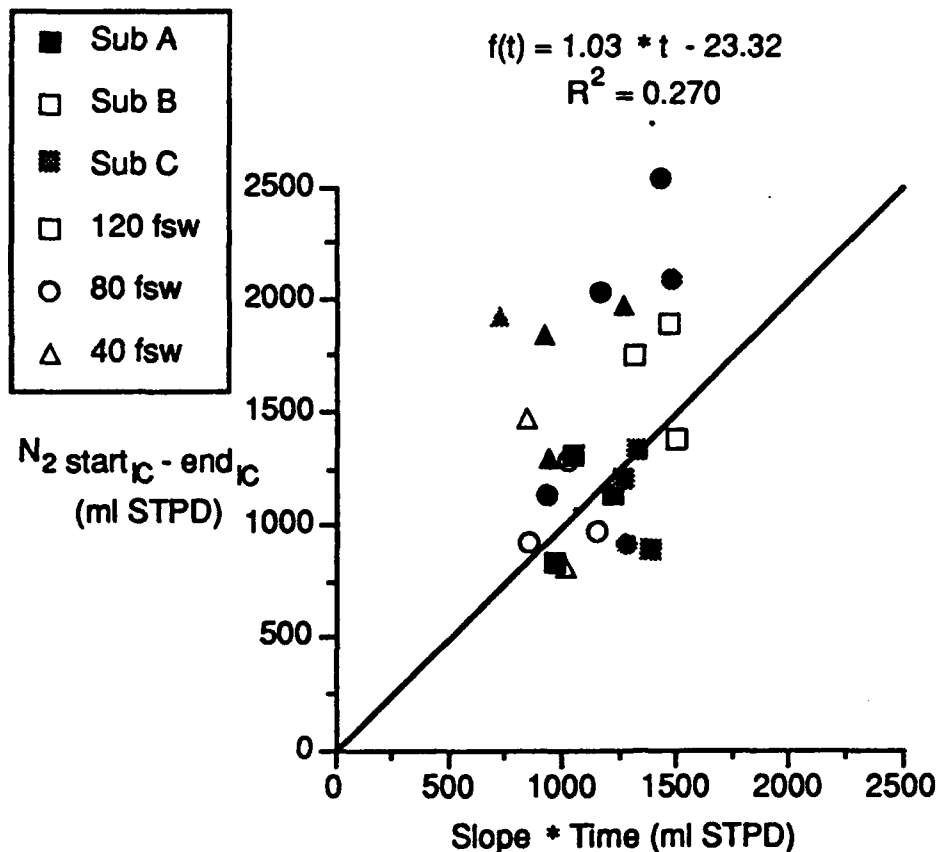


Figure 7: N₂ uptake volume comparison: N₂_{IC} vs Slope * Time

This scatter could be due to individual variability, error in reproducing IC, or measurement error in the breath-by-breath N₂ uptake measurements. IC measurements were not possible in 4 of the 2.21 ata experiments because total system volume decreased below the volume required for IC measurements. Both methods tend to underestimate the amount of N₂ uptake because neither takes into account the ~ 1 ml / min accumulation of water produced by CO₂ absorption in the circuit.

Figures 8 and 9 show raw breath-by-breath data recorded during typical experiments at each depth tested. Each point in the figures is the measured change in system N₂ volume from that which prevailed at run start for each successive breath ending at time t. Figure 9 shows an example of a discontinuity in the data which occurred during a 2.21 ata experiment when the subject inadvertently lost the mouthpiece. The first 13 minutes of data were offset by the mean difference of the 10 breaths before and after the discontinuity. Similar discontinuities occurred in 7 other experiments.

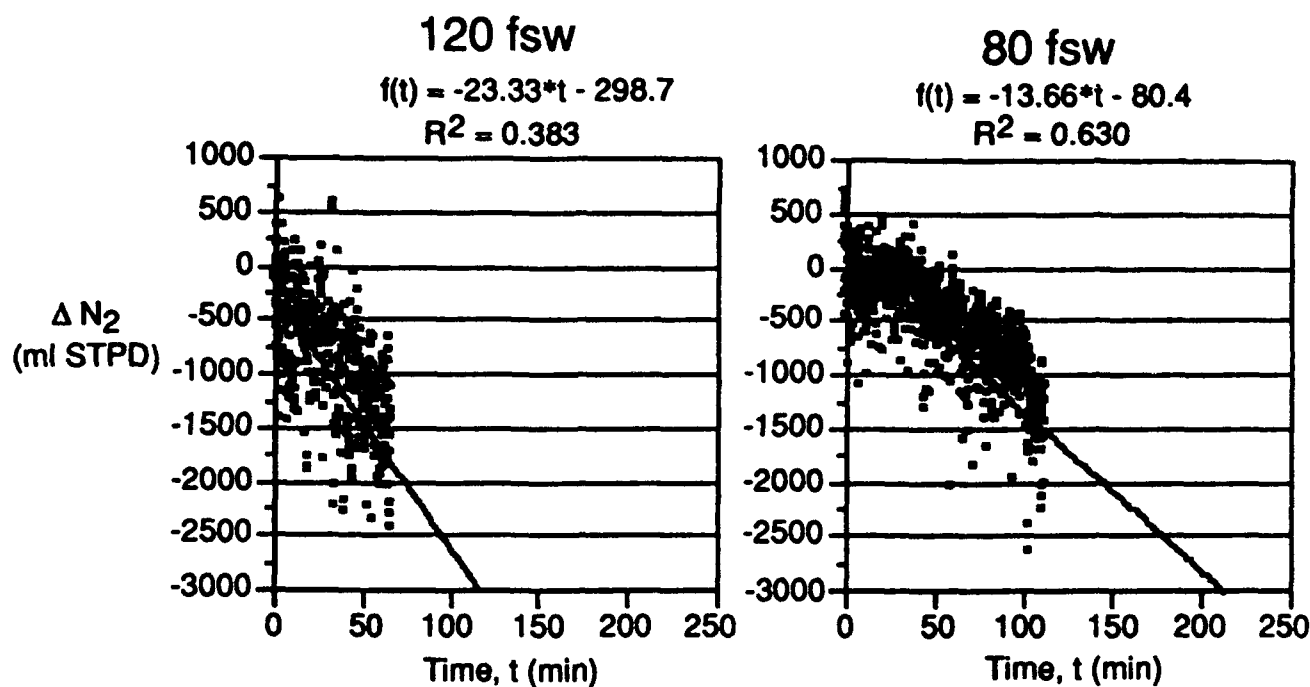


Figure 8 : N_2 volume change data from typical experiments at 120 fsw (4.64 ata) and 80 fsw (3.42 ata).

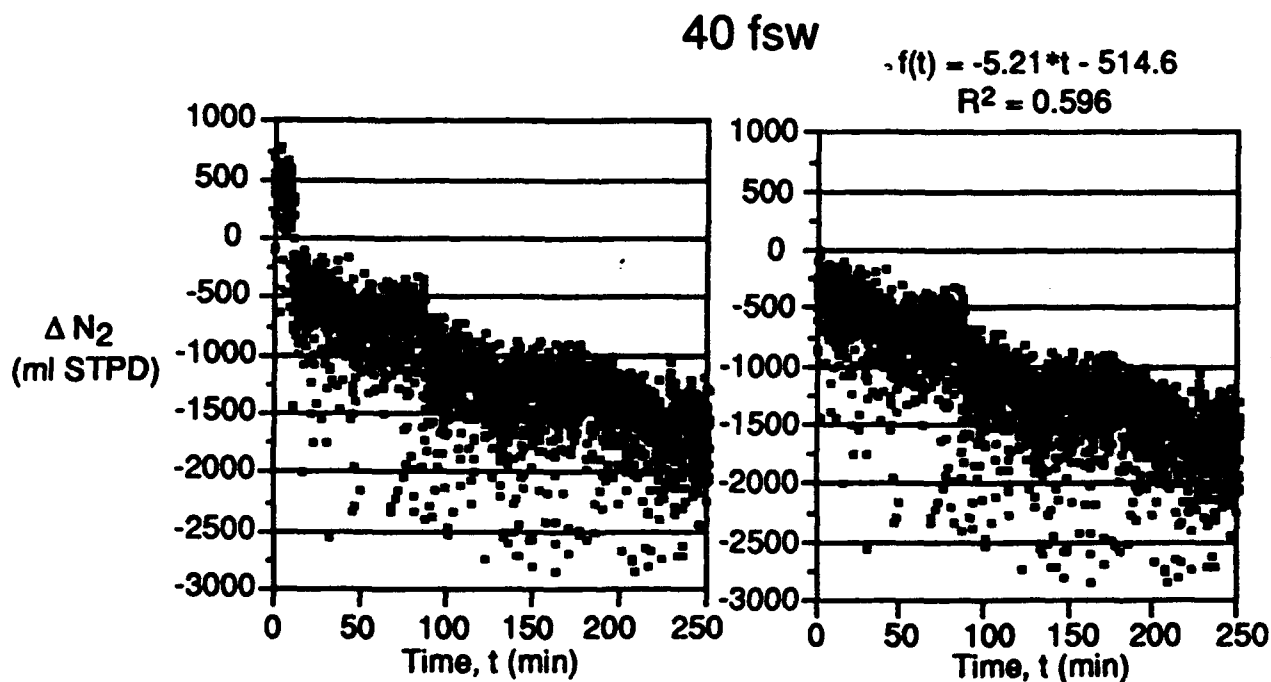


Figure 9 : N_2 volume change data from typical experiment at 40 fsw (2.21 ata). Note the discontinuity in the left panel. In the bottom panel, the first 13 minutes of data were offset by 500 ml to correct for an exhalation outside of the measurement system.

Non-zero intercepts (+222.9 in Figure 6, -298.7 and -80.4 in Figure 8, and -514.6 in Figure 9) indicate a change in the end-exhalatory volume from the first breath to most others, possibly resulting from a change in FRC. The intercept was calculated and used as an offset, added to each measured volume to correct for this artifact. Changes in system N₂ volume were transformed to reflect nitrogen uptake by subtracting each volume from zero. The resultant N₂ uptake volumes were normalized by dividing the volume of calculated nitrogen uptake by subject weight.

Based on the hypothesis that Henry's Law applies to whole-body equilibrium nitrogen content, respiratory N₂ uptake, V_{N₂}(t), may be expressed as:

$$V_{N_2}(t) = \alpha * \Delta P_{AN_2} * f(t) \quad (1)$$

where α is a proportionality constant equal to the whole-body N₂ solubility, ΔP_{AN_2} is the change in alveolar nitrogen pressure (from the surface to the depth of the experiment) and $f(t)$ is a function of time that defines the body response to a unit step change in alveolar N₂ pressure.

In order to cast the data into units of N₂ absorbed per unit change in alveolar N₂ pressure, measured breath-by-breath volumes were divided by the change in alveolar nitrogen pressure. The alveolar gas equation is shown below:

$$P_{AN_2} = F_{IN_2} * \{ (P_H - P_{H_2O}) - P_{CO_2} (1 - \frac{1}{RQ}) \} \quad (5)$$

where:

$$\begin{aligned} F_{IN_2} &= \left(\frac{P_{IN_2}}{P_H} \right) \\ P_{H_2O} &= 46 \text{ torr} \\ P_{CO_2} &= 45 \text{ torr} \\ RQ &= 0.85 \end{aligned}$$

$\Delta P_{AN_2} = 2.878 \text{ atm @ } 4.64 \text{ ata, } 1.913 \text{ atm @ } 3.42 \text{ ata, and } 0.957 \text{ atm @ } 2.21 \text{ ata}$

Random noise due primarily to tidal volume changes, obscured curvature in most profiles. The shorter, deeper experiments which were done first, yielded nitrogen

uptake profiles that were linear in appearance. Therefore, $f(t)$ was initially assumed to be a first-order linear equation. After substitution, Eq. (1) becomes:

$$V_{N_2}(t) = \alpha * \Delta P_{AN_2} * (\beta_0 + \beta_1 t) \quad (2)$$

where:

$V_{N_2}(t)$ = respiratory nitrogen uptake at time, t (ml / kg)

ΔP_{AN_2} = alveolar nitrogen pressure change (atm)

α = whole-body N_2 solubility (ml / kg • atm)

β_1 = rate of nitrogen uptake (ml / kg • min)

β_0 = intercept (ml / kg)

Rearrangement of Eq. (2) yields :

$$V_{N_2}(t) / \Delta P_{AN_2} = \alpha (\beta_0 + \beta_1 t) \quad (3)$$

First-order linear equations of the form shown in Eq. (3) were fit to the data. The slopes of the resultant lines corresponded to a N_2 uptake rate • solubility. Therefore, α could not be determined by this method. Intercept values were approximately zero, with $\alpha\beta_0 < 2.5$ ml/kg for all regression lines. Table 5 contains the approximate N_2 uptake rate-solubility products for each experiment, while Table 6 and Figure 10 show mean N_2 uptake rate-solubility products for each subject and depth.

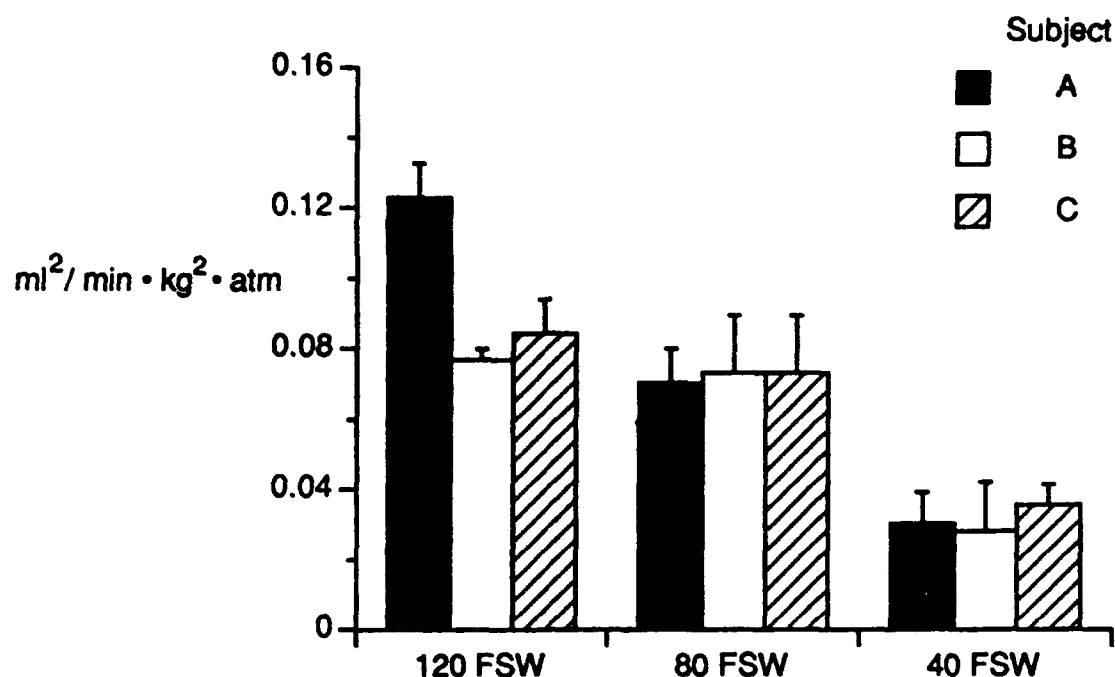


Figure 10 : Mean \pm SD slopes from linear regression about normalized data, $n = 3$ for each column

Table 5
N₂ uptake rate-solubility products from linear fits to data from each experiment

Depth (ata)	Subject A			Subject B			Subject C		
4.64	0.142	0.163	0.159	0.097	0.101	0.092	0.094	0.119	0.103
3.42	0.099	0.082	0.110	0.083	0.125	0.096	0.100	0.123	0.080
2.21	0.066	0.055	0.036	0.079	0.032	0.040	0.055	0.054	0.074

Table 6
Mean \pm SD N₂ uptake rate-solubility products from linear fits to data from each depth

Depth (ata)	Subject A	Subject B	Subject C
4.64	0.154 \pm 0.011	0.097 \pm 0.004	0.105 \pm 0.013
3.42	0.097 \pm 0.014	0.101 \pm 0.022	0.101 \pm 0.022
2.21	0.052 \pm 0.016	0.050 \pm 0.025	0.061 \pm 0.011

Figure 11 shows the linear regressions about data at each depth, while Figure 12 show a linear regression about all the data.

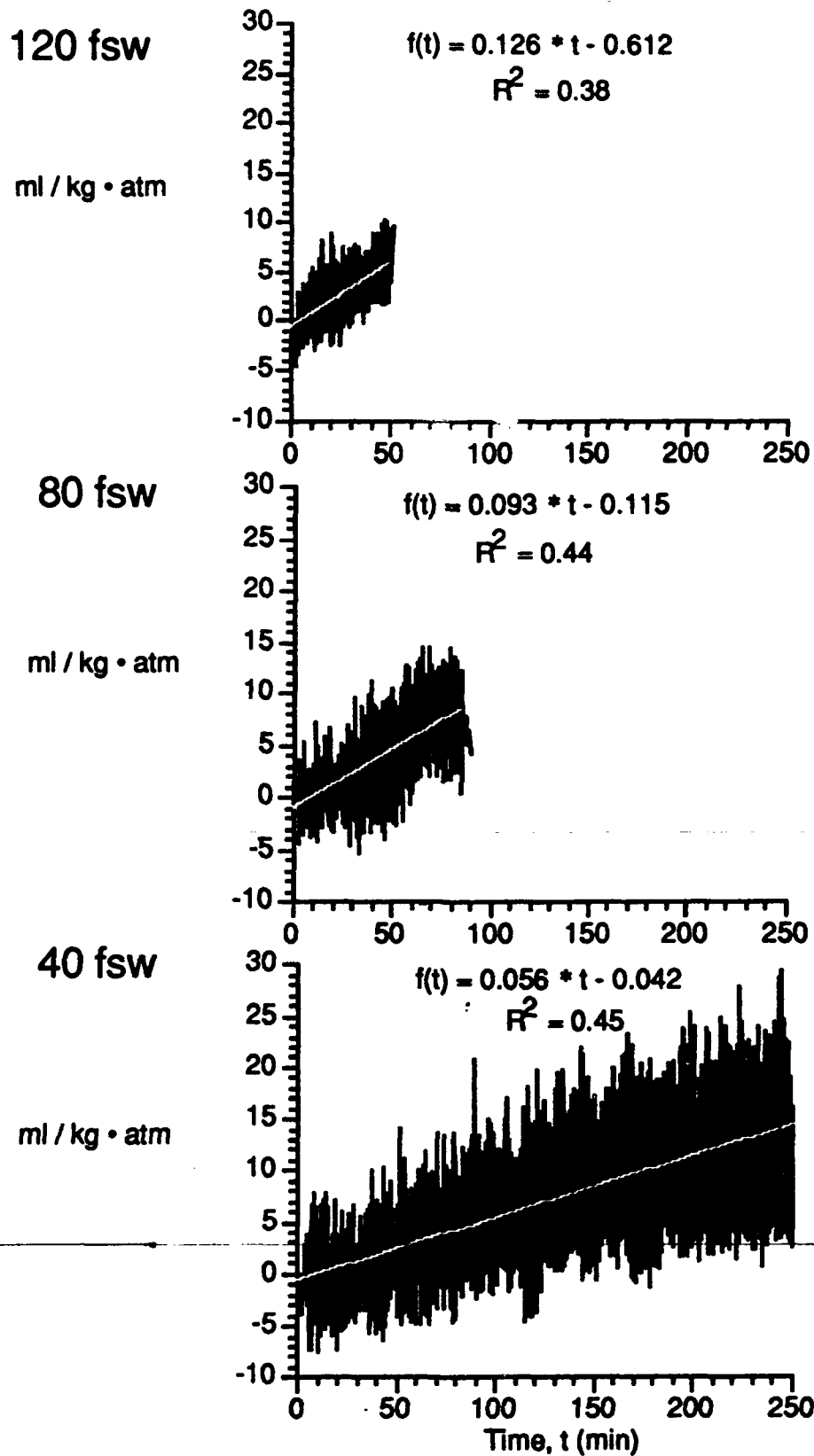


Figure 11 : Linear regression about data at each depth

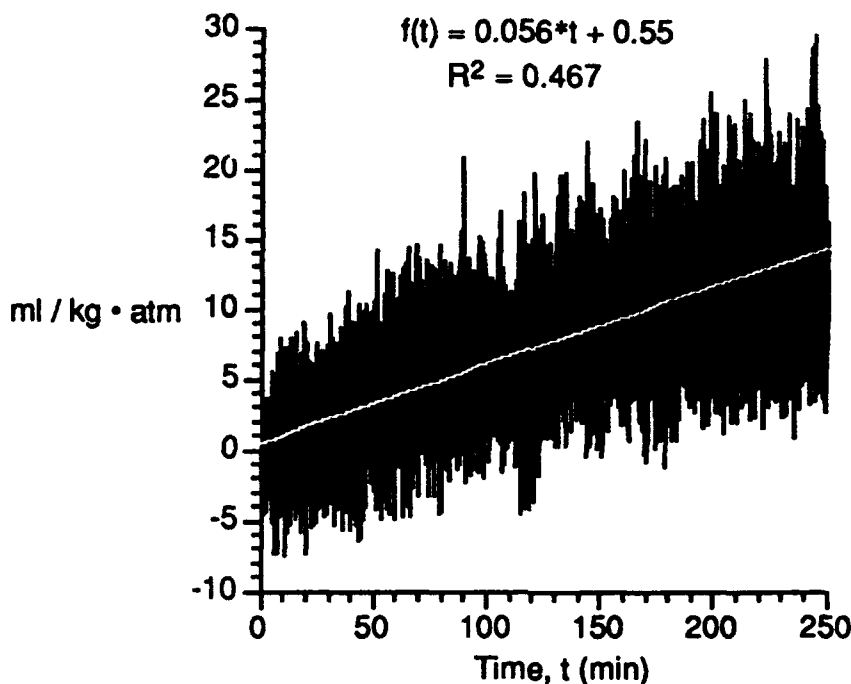


Figure 12 : Data from all depths with fitted Eq. (3)

The slope derived from the regression about all the data is the same as the slope from the 2.21 ata data. This result may be due to the longer duration and, therefore, the preponderance of 2.21 ata data. The R^2 values for the single-depth regressions (0.38 for 4.64 ata, 0.44 at 3.42 ata and 0.45 at 2.21 ata) are very similar to the R^2 value for the regression about the entire data set. All R^2 values were low signifying that considerable variation in the data remained which could not be accounted for by the model. There is nothing in the model, for example, to correlate breath-by-breath tidal volume changes.

The rate-solubility products at 4.64 and 3.42 ata were not significantly different from each other (paired t - test, $p < .05$) but were significantly higher than the corresponding product at 2.21 ata. The lower product for the longer 2.21 ata experiments indicates a trend toward saturation. To accommodate saturation behavior, a non-linear equation was fit to the data at each depth, with $f(t)$ assumed to

be of semi-exponential form, $(1 - e^{-kt})$ based on the Haldane model (15). Substitution into Eq. (1) gives :

$$V_{N_2}(t) = \alpha * \Delta P_{AN_2} * (1 - e^{-kt}) \quad (4)$$

and rearrangement yields :

$$V_{N_2}(t) / \Delta P_{AN_2} = \alpha * (1 - e^{-kt})$$

and

$$V_{N_2}(t) / \Delta P_{AN_2} = \alpha * (1 - e^{\frac{-0.693}{\tau} * t}) \quad (5)$$

where :

$V_{N_2}(t)$ = respiratory nitrogen uptake at time, t (ml / kg)

ΔP_{AN_2} = alveolar nitrogen pressure (atm)

α = whole-body N_2 solubility (ml / kg / atm)

τ = half-time (min)

Henry's Law is embodied in the $(\alpha * \Delta P_{AN_2})$ pre-exponential factor (amplitude) of Eq. (4). Significantly, whole-body N_2 solubility appears as an independent parameter in this equation, contrasting with its appearance as a parameter lumped with N_2 uptake rate in Eq. (2). Figure 13 shows the fit to the 2.21 ata data, while Table 7 shows that the fit failed to converge about the 3.42 and 4.64 ata data due to the lack of curvature in the short profiles.

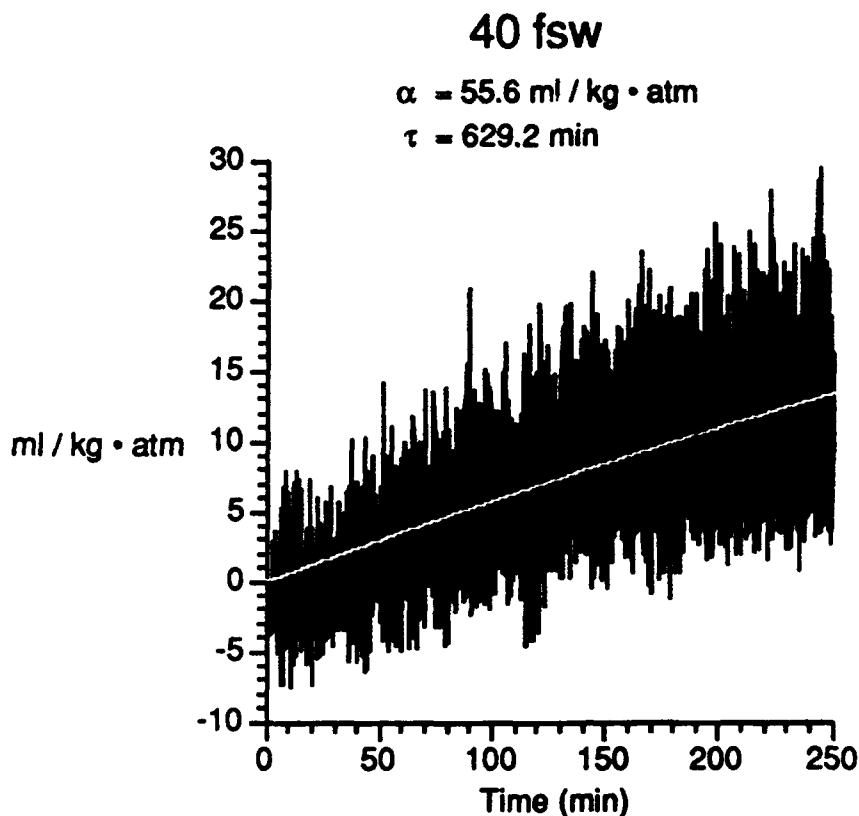


Figure 13 : Non-linear equation fit to 40 fsw data; 80 and 120 fsw data did not converge

Table 7
 Constants from non-linear regression about data from each depth

Depth ata	Time min	$\alpha \pm \text{SE}$ ml / kg·atm	$\tau \pm \text{SE}$ min
2.21	250	55.582 ± 7.443	629.19 ± 93.37
3.42	85	Did not converge	
4.64	50	Did not converge	

The non-linear equation was fit to the entire data set to test overall conformance to Henry's Law (Figure 14), resulting in the parameters given in Table 8.

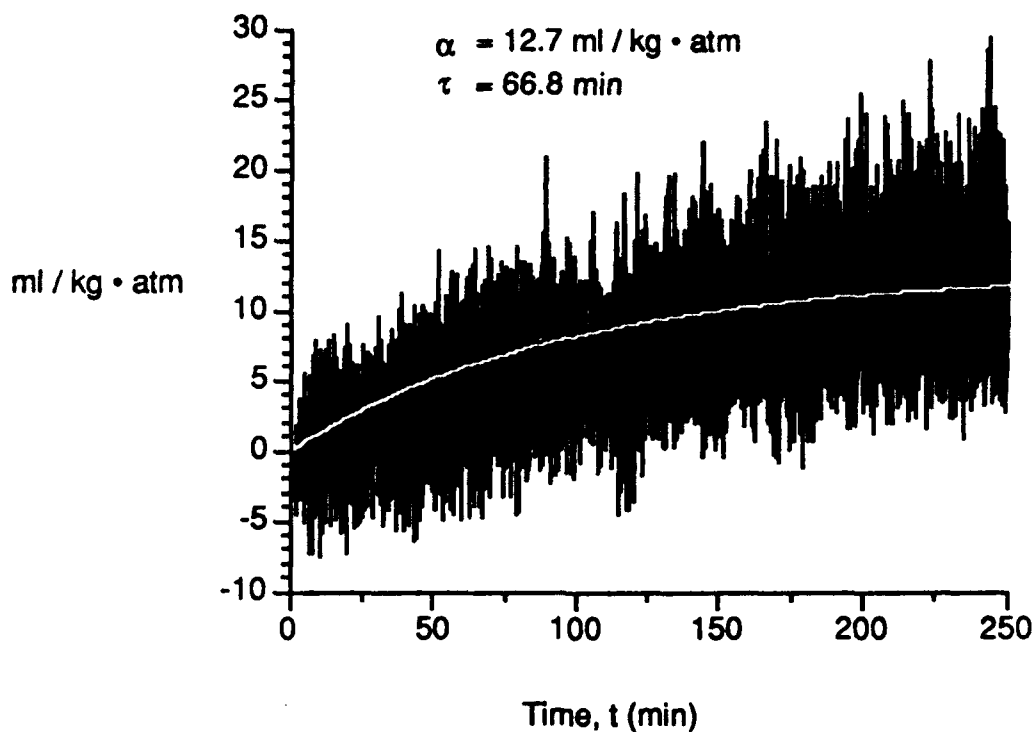


Figure 14 : Non-linear equation fit to combined data from all depths

Table 8
Constants from non-linear regression of Eq. (3) about all data

Depth ata	Time min	$\alpha \pm \text{SE}$ ml / kg • atm	$\tau \pm \text{SE}$ min
4.64	50	12.68 ± 0.13	66.76 ± 0.02
3.42	85		
2.21	250		

Resultant whole-body N_2 solubility ($0.01268 \text{ ml / gm} \cdot \text{atm}$) is comparable to that
for N_2 in water at 37°C , $0.01199 \text{ ml / gm} \cdot \text{atm}$ (15).

4. DISCUSSION

The measurement of respiratory nitrogen exchange with a closed-circuit rebreather is based upon the assumption that uptake of nitrogen from a subject's body manifests as a volume gain by the lungs and is reflected in turn as a loss in the rebreather counterlung, or spirometer. In the present system, carbon dioxide was scrubbed and oxygen was replaced as it was consumed. Therefore, the present rebreathing circuit was an open system for O_2 and CO_2 but was closed to N_2 except for the small amount of nitrogen exchange that might have occurred through the skin. Oxygen consumption did not change during the resting studies. Even if metabolic changes or changes in respiratory quotient had occurred, the volume of gas in the rebreather would not be affected. Because the system was open for O_2 , increased dissolved oxygen at increased inspired oxygen partial pressures had no effect on measured nitrogen volume changes in the system. Decreases in the total volume of the rebreathing circuit over time directly reflected the amount nitrogen taken up through the lungs.

The N_2 volume measurement system resolution (± 3 ml) was determined by unmanned tests at the surface. Boyle's law adjustments of measured volumes amplified measurement error at depth. System accuracy (within 5% of known volume changes) was determined by unmanned tests at the deepest depth investigated. Manned control measurements were deemed acceptable if N_2 volume measurement error was < 3.1 ml/min. First-order linear regressions about raw data from manned experiments at depth yielded N_2 volume changes ranging from 3.2 to 28.6 ml/min. During manned experiments, temperature, water vapor, CO_2 scrubbing and tidal volume variation introduced additional sources of error. These errors tend to be random and contribute only to a relatively large scatter in the results about a well-

behaved mean. Scatter in the data was typically ± 250 ml/atm. N_2 volume change measurements did not account for water accumulation due to CO_2 absorption (~ 1 ml/min), therefore, volume changes were underestimated.

Total N_2 volume decreases determined by multiplying the slopes of straight line fits to the breath-by-breath data by the experiment duration were validated in most cases by comparison to measured circuit volume changes over the entire course of each experiment. Overall N_2 volume changes were in the range of 600 - 2,000 ml for the profiles tested. Intra-subject variation ranged from 5 - 38 % with an average of 14.6 %.

N_2 volume change data were transformed to reflect N_2 uptake. First-order linear regressions about these data yielded rate-solubility products which approximated N_2 uptake. The rate-solubility products ($ml^2 / kg^2 \cdot atm \cdot min$) at 4.64 and 3.42 ata were not significantly different from each other but both were significantly different from those at 2.21 ata indicating that N_2 uptake kinetics were not linear functions of time. The curvature and lower rate of the 2.21 ata data indicated a trend toward saturation and suggested exponential rather than linear kinetics. The deeper dives were too short to exhibit this behavior.

The semi-exponential equation used to fit the data embodied Henry's Law and was Haldanian in form. The fit yielded whole-body nitrogen solubility and half-time as constants. This equation could be fit to the 2.21 ata data but would not converge about the 3.42 and 4.64 ata data due to their lack of curvature. Combining the data from all depths, the equation was fit to the data yielding a solubility of 0.0128 ml/gm \cdot atm which is very close to that of N_2 in water at 37° C water (0.01199 ml/gm \cdot atm).

Noise in the data obscured kinetic information concerning inert gas exchange in individual N_2 uptake profiles, but pooled data from multiple profiles yielded empirical support for the hypothesis that the pressure dependence of whole-body N_2 uptake in man is governed wholly by Henry's Law effects. A single semi-exponential equation

correlates measured whole-body N_2 uptake at pressures from 40 to 120 fsw. The resultant whole-body N_2 solubility is comparable to that for N_2 in water at 37° C.

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6. PUBLICATION(S)

Undersea and Hyperbaric Medicine. Abstract 75. v20 (Suppl.): 52.

NITROGEN UPTAKE DURING AIR DIVING. M.J. Natoli, W.A. Gerth, and R.D. Vann. F.G. Hall Hypo/Hyperbaric Center, Box 3823, Duke University Medical Center, Durham, NC 27710.

BACKGROUND: Henry's Law prescribes that the whole-body equilibrium N_2 content (C) will change in proportion to changes in the alveolar N_2 pressure (PA_{N_2}). How this effects N_2 uptake during air dives to different depths has never been empirically demonstrated in man.

METHODS: A computer controlled closed-circuit breathing apparatus was developed based on earlier work (Dick et al. UBR 11(4):369, 1984) and used to measure N_2 uptake in seated resting subjects during dives from sea level to 40 fsw for 250 min, 80 fsw for 85 min, and 120 fsw for 50 min. Each dive was followed by 60 min of O_2 decompression at 30 fsw. Air-equivalent inspired O_2 pressures were maintained and CO_2 was scrubbed. Decreases in circuit volume corresponding to N_2 uptake (ml STPD) were measured in real-time on a breath-by-breath basis and normalized to body weight. Three subjects (64.5, 71.7, and 95.6 kg) each dived to each depth three times for a total of 27 experiments. **RESULTS:** Noise in the data obscured the appearance of any curvature in the N_2 uptake profiles. Therefore, the following linear equation was fit to all the data from each depth:

$$VN_2(t) = \beta_1 \cdot \Delta PAN_2 \cdot t + \beta_0. \quad (1)$$

ΔPAN_2 was computed using the alveolar gas equation. Estimated rates of N_2 uptake (β_1 , ml/kg \cdot atm \cdot min) were 0.031 ± 0.001 at 40 fsw, 0.104 ± 0.002 at 80 fsw and 0.100 ± 0.003 at 120 fsw. All intercept values, β_0 , were less than 2.5 ml/kg. The lower rate (β_1) at 40 fsw indicated a trend toward saturation during the longer 40 fsw dives. Accordingly, Eq. (2), which accommodates saturation behavior and embodies Henry's Law ($\Delta C = \Delta PAN_2 \cdot \alpha$), could be fit to the 40 fsw data but would not converge about the 80 or 120 fsw data.

$$VN_2(t) = \Delta C \cdot (1 - \exp(-0.693 \cdot t/k)). \quad (2)$$

In order to test overall conformance to Henry's Law, Eq. (2) was fit to the data combined from all dives to all depths, yielding a whole-body N_2 solubility (α) of 6.47 ± 0.008 ml/kg \cdot atm and half-time (k) of 46.1 ± 0.02 min. **CONCLUSION:** Under the conditions studied, and to within present methodological precision, whole-body N_2 uptake follows the same kinetics, and pressure dependence is governed wholly by Henry's Law effects. Supported by ONR N00014-91-J-1763.

APPENDIX A :
DUKE UNIVERSITY MEDICAL CENTER
INSTITUTIONAL REVIEW BOARD PROTOCOL

DUKE UNIVERSITY MEDICAL CENTER INSTITUTIONAL REVIEW BOARD RESEARCH PROTOCOL

Complete and submit original and 2 copies to IRB (Room 107, Seeley G. Mudd Bldg., Box 3001) 15 days before scheduled meeting.

P.I. Richard D. Vann, Ph.D. ⁰²⁴⁶ M.D. 24R
Ph.D. Dept. Anesth. Phone 684-3300 PO Box 3001

Faculty Sponsor _____ Dept. _____ Phone _____ PO Box _____

Project Title Nitrogen uptake during air diving

Previous Registry # (Renewals) 03J-9J-1A1 Source of Research Funds U.S. Navy

Subject Types: ☒ Normal volunteers ☐ Subjects incapable of giving consent
(Check Types ☐ In patients ☐ Prisoners or institutionalized individuals
To Be Studied) ☐ Out patients ☐ Minors
☐ Patient controls ☐ Patient subjects over age 65
☐ Students

Does protocol call for:

Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Subject compensation? Patients \$ _____ Volunteers \$50/dive
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Investigational devices or drugs? If yes, study phase _____; letter of
<input type="checkbox"/>	<input checked="" type="checkbox"/>	More than minimal physical risk? _____ indemnification _____
<input type="checkbox"/>	<input checked="" type="checkbox"/>	More than minimal psychological stress?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Confidential material (questionnaires, photos, etc.)?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Extra costs to the subjects (tests, hospitalization, OPC visits)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	The exclusion of pregnant women?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is blood used? Give total amount _____ over time period _____ (Days)

Are the following used? If yes, obtain appropriate signatures:

Yes	No		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	VA Hospital	VA IRB
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Rankin Ward	Clin. Res. Unit Comm.
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Jordan Ward	Ca. Res. Unit Comm.
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Hypo/Hyperbaric Unit <u>RD Vann</u>	Safety Comm.
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Radiation (ionizing, laser)	Radiation Comm.
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Operating Room or Anesthesia Time	Minutes required

The following signatures are required before submission to the IRB:

P.I. (and faculty sponsor)	<u>RD Vann</u>	Date	<u>12/3/90</u>
Dept. IRB Member (Clinical Dept.)	<u>[Signature]</u>	Date	<u>12/15</u>
Dept. Chairperson	<u>[Signature]</u>	Received	Signed
		Date	<u>12/18</u>
		Received	Signed

DO NOT WRITE BELOW THIS LINE

Assigned IRB Member [Signature]
IRB Action: ☒ Approved ☐ Tabled ☐ Disapproved
☐ Approved with modification
Approval Termination Date 1/10/92 Registry # Assigned 024-91-1R2

IRB Chairperson

Date of Approval

Rev. 11/86

Briefly summarize your protocol below (no more than two pages). The summary should include applicable items in the check list under description of the protocol. Additional material may be appended but the brief summary must be provided. Append a consent form. Refer to checklists for content of protocol and consent forms.

This study has not been activated but there have been changes in the planned experimental procedure from the previous protocol. These changes were submitted and approved by Dr. Jerome Harris in October 1989 and are reproduced below.

The techniques for measuring respiratory nitrogen exchange are non-invasive and essentially unchanged. Subjects will breathe from a closed-circuit system which removed carbon dioxide and maintains a constant 21% oxygen level. Subjects will be seated in a body plethysmograph to allow independent measurement of respiratory function which is needed for nitrogen exchange calculations. This will replace the fabric bands around the chest and abdomen discussed in the original protocol.

Nitrogen uptake will be measured at three depths from air breathing subjects who are seated at rest. Three subjects will be studied and nitrogen uptake will be measured three times at each depth for every subject to examine the consistency of gas uptake. Experiments will be conducted approximately once a week over a 12 month period.

All experiments will be followed by 60 min of oxygen breathing at 30 fsw for decompression. The estimated risk of decompression sickness for these exposures is less than 0.1%. The depths and bottom times from which the three experimental dives will be selected are:

<u>Depth (fsw)</u>	<u>Time (min)</u>
40	300
50	190
60	140
70	110
80	90
90	80
100	70
110	65
120	60

These dives were chosen by the same method used to compute decompression procedures employed over the past two years in an underwater archeology project. This project, under the direction of the Institute of Nautical Archeology (Texas A & M), is excavating a 3,000 year old shipwreck off the coast of Turkey. In nearly 5,000 repetitive dives, there have been only two cases of pain-only bends (0.04% DCS incidence). The dives were to depths of 150-180 fsw with 20 min bottom times separated by a 5 hr surface interval.

All protocols are approved for a maximum of one year. Research must stop at the end of one year unless the protocol is reapproved for another year. Unexpected, unusual or serious complications or an unanticipated frequency of reactions during the course of a clinical investigation must be reported immediately, and in detail, to the IRB and your department chairperson.

INCLUDE THE ASSIGNED PROTOCOL NUMBER IN ALL CORRESPONDENCE WITH THE IRB CONCERNING THE PROTOCOL.

Subjects will be drawn from among laboratory personnel or from the local community. Subject compensation will be \$50 per study. As before, subjects will be briefed concerning the goals and risks of the study but will not be required to be trained divers. A tender from among laboratory personnel will be present in the chamber during all dives. The tender will breathe a higher oxygen percentage than the subject to lower his nitrogen uptake on the bottom and his subsequent DCS risk. This will be done because the tenders will make more dives than will the subjects.

After decompression, the subjects will be monitored for precordial bubbles with Doppler. If Grade III or IV bubbles are detected, extra oxygen will be added to subsequent decompressions. In the unlikely event that decompression sickness should occur, subjects will be treated in accordance with best diving medical practice by the on-call Divers Alert Network diving physician.

DO NOT DETACH.

INCLUDE THE ASSIGNED PROTOCOL NUMBER IN ALL CORRESPONDENCE WITH THE IRB CONCERNING THE PROTOCOL.

DUKE UNIVERSITY MEDICAL CENTER
INFORMED CONSENT FORM - PART I

Clinical Investigation

Consent to Participate in Research Study

IRB # _____

PROTOCOL TITLE Nitrogen uptake during air diving

The chambers at the F.G. Hall Laboratory can be used to simulate various depths beneath the seas by pumping air into the chambers and thus increasing atmospheric pressure. They can also be used to simulate various heights above the earth by sucking air out of the chambers and thus decreasing atmospheric pressure. Exposure to such changed atmospheric pressures will involve changes in pressure both inside and outside the body. The potential hazards of such exposures may be outlined as follows:

1. Hazards associated with compression or increasing the air pressure inside the chambers (simulation of depths beneath the sea or rapid return to the surface from simulated altitude):

With compression there is occasional difficulty getting the air pressure in the ears, sinuses, teeth, lungs and intestines to equal the increasing pressure outside the body. Such problems may cause pain and the production of fluid in these spaces. Hearing loss, inflammation of the ear and sinusitis may occur. Usually, these problems are temporary and clear in a few days. Very rarely permanent problems occur. However, if any discomfort is felt during compression, the personnel in the laboratory should be immediately notified so that corrective measures can be taken. Occasionally individuals have air filled cysts in their lungs. If such a person is exposed to increased pressure, the cyst could possibly rupture and cause the lung to collapse, requiring medical and/or surgical treatment such as inserting a tube through the skin into the chest to re-expand the collapsed lung. This complication is rare and, thus far has not occurred in this laboratory in greater than 20 years of experience involving thousands of patient exposures.

2. Risks associated with decreases in air pressure or decompression from simulated depths beneath the sea:

With a decrease in air pressure such as is encountered during decompression from simulated depths, or exposure to simulated altitudes, symptoms such as pain, weakness, or paralysis can occur and are termed decompression sickness. The cause is thought to be the formation of gas bubbles in the body. These bubbles can cause damage to the brain, spinal cord, death and disability. In this laboratory, the depth as well as the rate of changes in pressure are carefully controlled, and only mild and transient forms of decompression sickness have been seen here.

Early symptoms of bubbles may be pain in the joints, skin rash or, if an individual has had migraine in the past, a migraine headache. If these symptoms occur, either during the test or (and this is important) at any time after the test, the Hall Laboratory personnel should be notified immediately by calling (919) 684-8111 and asking for the hyperbaric physician on call, for many, but not all, cases of decompression sickness can be cured by prompt recompression.

Also with decompression, lung air sacs may rupture with gas bubbles occurring in the chest, neck and blood. The gas bubbles may travel through the arteries and cause a blockage of the arteries supplying the heart, brain or other organs. heart attack or stroke may occur. This problem is termed air embolism; it is

INFORMED CONSENT FORM - PART I

Clinical Investigation

Consent to Participate in Research Study

IRB # _____

PROTOCOL TITLE Nitrogen uptake during air diving

rarely encountered in chamber exposures and has not been seen therefore in the Duke chambers.

3. Other hazards associated with exposures to increased atmospheric pressures (simulated depths beneath the sea):

Exposure to higher than normal oxygen concentrations can cause generalized shaking and even seizures. If a potentially hazardous exposure to an increased amount of oxygen is part of the experiment, the details and risks are thoroughly reviewed beforehand with the subject and are contained in Part II.

An additional potential hazard associated with exposure to increased atmospheric pressure is destruction of certain parts of long bones. Experts generally agree that this problem is exceedingly rare with exposures to simulated depths of less than 100 feet and/or for exposure times not exceeding three to four hours.

4. Risks associated with exposure to simulated altitudes (sucking air out of the chambers):

Individuals exposed to simulated altitudes, decreased atmospheric pressures, can become unconscious and seriously harmed if the amount of oxygen available for breathing becomes too low. If a test exposure to a less than normal amount of oxygen is part of the experimental design, the investigator reviews thoroughly beforehand with the subject the details and risks of the experiment. The details and risks are contained in Part II. If an individual during an exposure to simulated altitude feels lightheaded or notices any discomfort or unusual sensations, he should notify the chamber personnel immediately. Also, decompression sickness as noted above can occur with altitude exposure. This complication is unusual. If an individual develops signs or symptoms of low oxygen or decompression sickness during altitude exposure, the chamber might have to be recompressed or returned to the surface rapidly. This rapid increase in chamber pressure would expose individuals to increased risks of equalizing air pressure in the ears, sinuses, teeth, intestines or lungs with possible injury to these structures as noted above in the discussion of hazards of compression or increasing the air pressure inside the chambers. These complications are unusual.

5. Risks associated with equipment failure:

If there is mechanical or electrical failure of part of the pressure tank or of the equipment which keeps it operating safely, the exposed humans could be seriously injured or even killed. If a fire occurs within the pressure tank, all exposed humans could be burned or asphyxiated. In over twenty years of operation, there have not been any instances of structural failure or fire in the Duke chambers. Moreover, all new equipment is subjected to evaluation and testing before its use is permitted in the chamber. A regular preventive maintenance program is utilized for all systems. Nonetheless, the possibility of equipment failure, however remote, cannot be completely eliminated.

DUKE UNIVERSITY MEDICAL CENTER
INFORMED CONSENT FORM - PART 1

CLINICAL INVESTIGATION

Consent to Participate in Research Study

IRB # _____

Protocol Title Nitrogen uptake during air diving

6. General risks:

It is important that individuals about to undergo tests involving the changing atmospheric pressures understand that many of these tests have never been performed under such conditions before and there may be risks which are unknown. If all was known about what happened or what might happen, there would be no reason to do the tests. Investigators have been instructed to answer any questions concerning risks and safety measures. Individuals about to undergo such tests should also understand that the test should not be done if their consent has been effected by a promise of a large sum of money or by other pressures to participate.

7. Provision of care:

Immediate necessary care is available if an individual is injured because of participation in this research project. However, there is no provision for free medical care or for monetary compensation for such injury. Further information concerning this and the rights of subjects in research can be obtained from the Hospital Risk Management Office, 684-3277.

8. For women of childbearing potential:

There is evidence to support that the frequency of birth defects is significantly greater among children from pregnancies during which women have been exposed to increased pressures as for example in diving.

It is therefore necessary that a pregnancy test be done first on women of childbearing potential. The performance of this test requires using 2 teaspoons of blood drawn from my vein by a needle stick. To my knowledge I am not pregnant at the present time. Further, if sexually active, I will take contraceptive precautions for the duration of this research.

9. Statement by subject:

I have read Parts I and II of this Informed Consent and have been given the opportunity to discuss this experiment and to ask questions. I have been informed that I may contact Dr. Richard Vann at 684-3305 to answer
(Investigator) (telephone #)

any questions I may have during this investigation. I agree to participate as a subject with the understanding that I may withdraw at any time except for the necessity of staying in the chamber for the time required for decompression.

Signature

Date

Person obtaining consent

Date

DUKE UNIVERSITY MEDICAL CENTER

Form
M 03

Informed Consent (Part II)

Nitrogen uptake during air diving.
IRB Research Protocol No. _____

We are asking you to take part in a research study at the F.G. Hall Laboratory for Environmental Research, Duke University Medical Center. It is important that you read and understand several general principles that apply to all who take part in these studies:

- a) Taking part in this study is entirely voluntary.
- b) Personal benefit may not result from taking part in this study, but knowledge may be gained that will benefit others.
- c) You may refuse to participate or may withdraw from the study at any time.
- d) There will be no charge to you for the research procedures.
- e) When the results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records are maintained according to hospital requirements.
- f) Should you have any questions with regard to this research, you are urged to contact Dr. Richard Vann at 684-3305.
- g) Any significant new findings developed during the course of this research, which may bear upon your willingness to continue participation in the research, will be provided to you.
- h) Research Related Injuries: Immediate necessary care is available if an individual is injured because of participation in a research project. However, there is no provision for free medical care or for monetary compensation for such injury. Further information concerning this and the rights of subjects in research can be obtained from the Hospital Risk Management Office at 684-5280.

The air we breathe is a mixture of oxygen and nitrogen. The oxygen is used up to keep us alive, but the nitrogen dissolves in the tissues and remains there just as carbon dioxide dissolves in soda. During diving or altitude exposure, nitrogen moves into and out of the body through the lungs in response to changes in pressure. If the pressure is reduced too rapidly, the gases dissolved in the tissues can form bubbles and cause decompression sickness.

The object of the experiments for which you are volunteering is to measure the movement of nitrogen through your lungs during compressed air diving. Nine experiments are planned ranging in total time from 2-6 hours. These experiments include dives to pressures equivalent to seawater depths of 40 to 120 feet. While at these depths, you will sit at rest inside a sealed box to

Initials of Subject

DUKE UNIVERSITY MEDICAL CENTER

Form
M-03

Informed Consent (Part II)

Nitrogen uptake during air diving.

IRB Research Protocol No. _____

allow your lung volume to be measured. The box will be in a pressure chamber. You will wear nose clips and breathe through a mouthpiece into a device which measures the volume of nitrogen that enters or leaves your body. There is mild discomfort associated with the noseclips and mouthpiece, but this discomfort is minimal.

While the pressure in the chamber is increasing, it will become warm, and you will have to equalize the pressure in your ears as sometimes occurs during aircraft travel. When the pressure decreases, the chamber will become cool. At depths of about 100 feet or deeper, you may notice a slight light-headedness. This is known as nitrogen narcosis and will disappear upon return to sea level pressure.

At the end of the nitrogen exchange measurements, the chamber pressure will be reduced to 30 feet. You will leave the sealed box and breathe oxygen for 60 minutes to eliminate nitrogen that has accumulated in your body. This reduces, but does not eliminate, the risk of decompression sickness. The estimated chances that you will develop decompression sickness are less than 0.1%, but should this occur, you will be recompressed in the chamber while breathing 100% oxygen under the supervision of a diving physician. This is an effective treatment which usually eliminates all symptoms of decompression sickness. These symptoms were described in Part I of this Informed Consent which you have read.

You will be accompanied while in the chamber by an attendant. After your dives, he will place an instrument over your heart to listen for gas bubbles. These bubbles are not uncommon after diving and the procedure for detecting them is painless. You will receive a physical examination before beginning your dives.

"I have read the above and understand the discomforts, inconveniences, and risks of this study. I have been given the opportunity to discuss it and to ask questions. I agree to participate as a subject with the understanding that I may withdraw at any time without prejudice."

Date

Signature of Subject

Date

Person obtaining consent

APPENDIX B :

ESTIMATION OF DECOMPRESSION RISK

The statistical analysis of decompression data and the quantitative estimation of decompression risk have become practical realities since introduction of the method of maximum likelihood (Weathersby et al. 1984). Likelihood analysis is implemented by formulating a mathematical model which relates environmental and physiological variables such as time, pressure, work, immersion, oxygen breathing, and temperature to some measure of decompression stress. While empirical models are often employed, we believe the results can be more satisfactory if fundamental decompression mechanisms such as bubble formation, inert gas exchange, and symptom origin are included.

Decompression mechanisms are incompletely understood, however, and a variety of models can be constructed from alternative hypotheses. Likelihood analysis provides an objective means for differentiating between hypotheses. Analysis of a given dataset by a specific model results in a characteristic maximum likelihood which measures how well the model corresponds to the data. Other models will have different maximum likelihoods. A model with a statistically larger maximum likelihood is a better choice for computing decompression risk and may have greater physiological validity. In addition, specifically recognizable deficiencies of a physiological model can suggest circumstances in which derived decompression procedures might be unreliable.

The basic assumption of our modeling efforts is that all forms of decompression sickness are initiated by bubbles. Models currently under investigation assume that pain-only DCS results from stationary extravascular bubbles (Vann et al. 1990). (To describe chokes, spinal, and cerebral symptoms, different models probably will be necessary.) Upon decompression, bubbles grow to a maximum volume and resolve as nitrogen diffuses between the bubble and tissue (Fig. 1).

A current working hypothesis is that DCS occurs when the maximum bubble volume exceeds a critical value. Each individual in a population is assumed to have his own characteristic critical volume. The critical volume of a population is described by a density function such that the largest fraction of the population develops DCS at intermediate volumes while smaller fractions are susceptible at low or high volumes (Fig. 2).

The estimated risk of a decompression procedure is the fraction of the population for whom the critical volumes are exceeded. If a decompression procedure has a maximum bubble volume V_{max} , for example, the risk is the area under the density function (the integral) to the left of V_{max} (Fig. 2). The integral of the population density function defines DCS risk as an explicit function of bubble volume (Fig. 3).

The experimental dive profiles are based on a three-tissue model (Fig. 4) in which risk is determined by the volume of the largest bubble (Vann 1987, 1990). Inert gas exchange between blood and tissue is assumed to be perfusion-limited as in a Haldane tissue compartment. A bubble, however, is surrounded by a diffusion barrier, and its growth is limited by both perfusion and diffusion. Bubble growth by diffusion is a gradual process consistent with the commonly observed delay in symptom onset.

The response of a bubble to a dive profile is controlled by the model parameters: blood flow, tissue volume, elastic tissue pressure, diffusion barrier permeability, and blood and tissue nitrogen solubilities. The values of these parameters are determined by the best correspondence (or fit) between the predictions of the model and a body of experimental data. This correspondence is found by the method of maximum likelihood.

The experimental data used to develop the current risk estimates were trials of the U.S. Navy Standard Air Decompression Table representing 568 man-tests of 88 single-dive schedules in which there were 27 DCS incidents (Des Granges 1957). These incidents were of unspecified nature but sufficiently severe to require recompression in an era where mild

symptoms frequently went untreated. The water temperature was generally comfortable, and the divers exercised by swimming or weight lifting.

Estimating the risk of oxygen decompression from the Des Granges air trials is not unlike predicting tomorrow's weather from last year's observations. The risks of the nitrogen uptake dive profiles, therefore, are extrapolations which are relative rather than absolute measures of risk.

Because of the extrapolation uncertainties, dive profiles were developed with the rather low estimated risk of 0.01%. This was found to produce conservative procedures when applied to dives for which human exposure data are available. Oxygen decompression procedures calculated by these methods and used in other projects have proven reasonably satisfactory. These projects are described in the enclosures to this appendix.

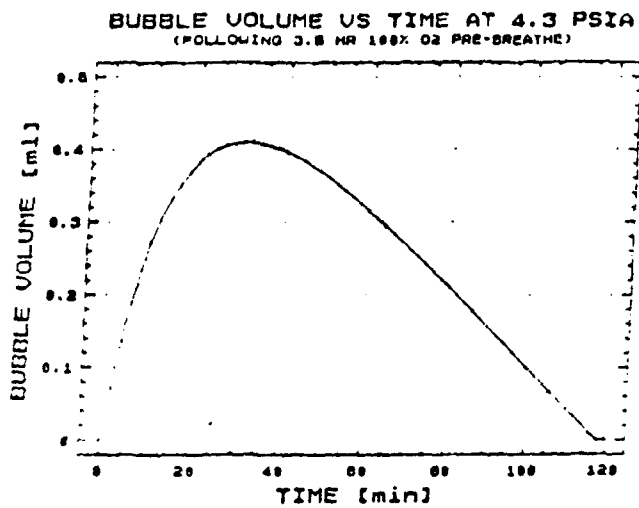
Other decompression models and databases are under investigation, and the results of these investigations will be used to update the current risk estimates. The mechanisms of bubble formation, the number and arrangement of the tissues involved in inert gas exchange, and the mathematical details of this exchange will be evaluated. As part of this work, statistical procedures will be developed for determining confidence limits on risk estimates.

References

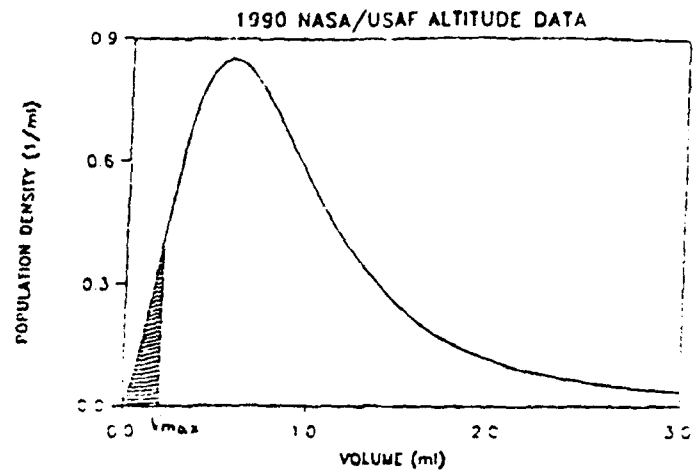
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- Weathersby, P.K., L.D. Homer, and E.T. Flynn. 1984. On the likelihood of decompression sickness. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 57(3): 815-825.

Figures

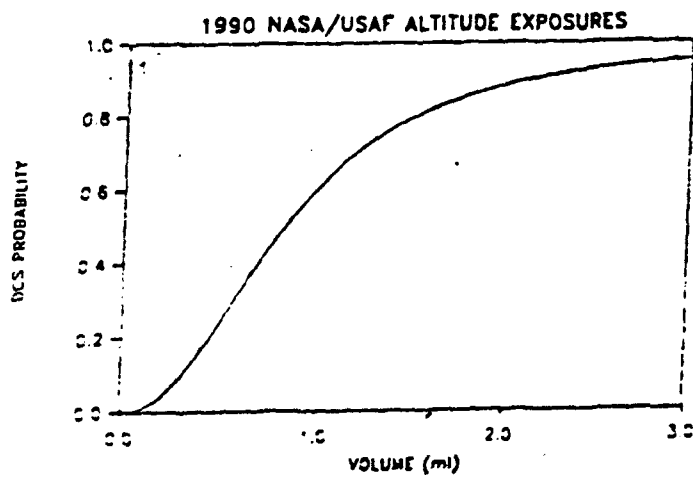
1. Bubble growth.



2. Density of critical volume.



3. Density function integral.



4. Three tissue model.

